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(54) **MANGANESE COMPLEXES OF NITROGEN-CONTAINING MACROCYCLIC LIGANDS EFFECTIVE AS CATALYSTS FOR DISMUTATING SUPEROXIDE**

MANGAN-KOMPLEXE VON STICKSTOFF-ENTHALTENDEN MACROZYKLISCHEN LIGANDEN UND IHRE VERWENDUNG ALS SUPEROXIDDISMUTASE KATALYSATOREN

COMPLEXES MANGANESIENS DE LIGANDS MACROCYCLIQUES CONTENANT DE L'AZOTE ET EFFICACES COMME CATALYSEURS POUR LA DISMUTATION DU SUPEROXYDE

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## Description

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

The present invention relates to compounds effective as catalysts for dismutating superoxide and, more particularly, relates to manganese(II) or manganese(III) complexes of nitrogen-containing sixteen-membered macrocyclic ligands which catalytically dismutate superoxide.

#### 2. Related Art

The enzyme superoxide dismutase catalyzes the conversion of superoxide into oxygen and hydrogen peroxide according to equation (1) (hereinafter referred to as dismutation). Reactive oxygen metabolites derived from superoxide are postulated to contribute to the tissue pathology in a number of

$$O_2^{\dot{-}} + O_2^{\dot{-}} + 2H+ \Rightarrow O_2 + H_2O_2 \qquad (1)$$

inflammatory diseases and disorders, such as reperfusion injury to the ischemic myocardium, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, atherosclerosis, hypertension, metastasis, psoriasis, organ transplant rejections, radiation-induced injury, asthma, influenza, stroke, burns and trauma. See, for example, Simic, M. G., et al, Oxygen Radicals in Biology and Medicine, Basic Life Sciences, Vol. 49, Plenum Press, New York and London, 1988; Weiss J. Cell. Biochem., 1991 Suppl. 15C, 216 Abstract C110 (1991); Petkau, A., Cancer Treat. Rev. 13, 17 (1986); McCord, J. Free Radicals Biol. Med., 2, 307 (1986); and Bannister, J.V. et al, Crit. Rev. Biochem., 22, 111 (1987).

It is also known that superoxide is involved in the breakdown of endothelium-derived vascular relaxing factor (EDRF), which has been identified as nitric oxide (NO), and that EDRF is protected from breakdown by superoxide dismutase. This suggests a central role for activated oxygen species derived from superoxide in the pathogenesis of vasospasm, thrombosis and atherosclerosis. See, for example, Gryglewski, R.J. et al., "Superoxide Anion is Involved in the Breakdown of Endothelium-derived Vascular Relaxing Factor", *Nature,* Vol. 320, pp. 454-56 (1986) and Palmer, R.M.J. et al., "Nitric Oxide Release Accounts for the Biological Activity of Endothelium Derived Relaxing Factor", *Nature,* Vol. 327, pp. 523-26 (1987).

Clinical trials and animal studies with natural, recombinant and modified superoxide dismutase enzymes have been completed or are ongoing to demonstrate the therapeutic efficacy of reducing superoxide levels in the disease states noted above. However, numerous problems have arisen with the use of the enzymes as potential therapeutic agents, including lack of oral activity, short half-lives *in vivo,* immunogenicity with nonhuman derived enzymes, and poor tissue distribution.

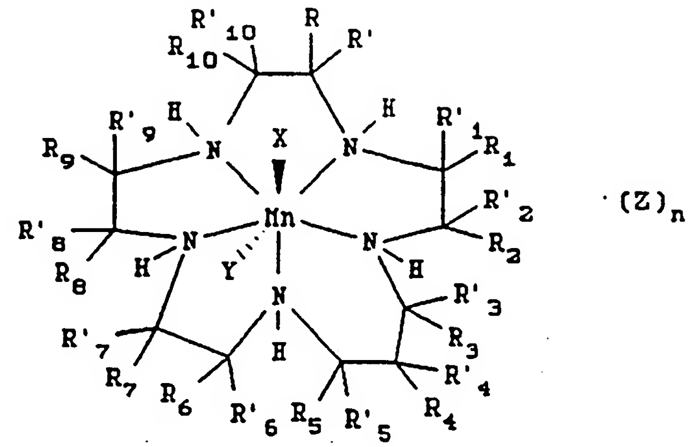
In European patent application EP-0,524,161-A1, filed earlier but published after the priority date of the present patent application, compounds effective as catalyst for dismutating superoxide have been disclosed. These compounds are manganese (II) and manganese (III) complexes of nitrogen-containing fifteen-membered macrocyclic ligands which catalyze the conversion of superoxide into oxygen and hydrogen peroxide. These compounds are low molecular weight mimics of superoxide dismutase which are useful as therapeutic agents for inflammatory desease states and disorders which are mediated by superoxide.

### SUMMARY OF THE INVENTION

The present invention is directed to low molecular weight mimics of superoxide dismutase (SOD) useful as therapeutic agents for inflammatory disease states and disorders which are mediated, at least in part, by superoxide. The SOD mimics of the present invention are manganese(II) or manganese(III) complexes of nitrogen-containing sixteen-membered macrocyclic ligands.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to manganese(II) or manganese(III) complexes of nitrogen-containing sixteen-membered macrocyclic ligands which catalyze the conversion of superoxide into oxygen and hydrogen peroxide. These complexes can be represented by the formula:



wherein R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ independently represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; $R_1$ or $R'_1$ and $R_2$ or $R'_2$, $R_3$ or $R'_3$ and $R_4$ or $R'_4$, $R_3$ or $R'_3$ and $R_5$ or $R'_5$, $R_4$ or $R'_4$ and $R_5$ or $R'_5$, $R_6$ or $R'_6$ and $R_7$ or $R'_7$, $R_8$ or $R'_8$ and $R_9$ or $R'_9$, and $R_{10}$ or $R'_{10}$ and R or R' together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R or R' and $R_1$ or $R'_1$, $R_2$ or $R'_2$ and $R_3$ or $R'_3$ or $R_4$ or $R'_4$, $R_4$ Or $R'_4$ or $R_5$ or $R'_5$ and $R_6$ or $R'_6$, $R_7$ or $R'_7$ and $R_8$ or $R'_8$, and $R_9$ or $R'_9$ and $R_{10}$ or $R'_{10}$ together with the carbon atoms to which they are attached independently form a nitrogen containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', $R_1$ and R'1, $R_2$ and $R'_2$, $R_3$ and $R'_3$, $R_4$ and $R'_4$, $R_5$ and $R'_5$, $R_6$ and $R'_6$, $R_7$ and $R'_7$, $R_8$ and $R'_8$, $R_9$ and $R'_9$, and $R_{10}$ and $R'_{10}$ together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; and one of R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ together with a different one of R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations thereof. Thus, the complexes of the present invention can have any combinations of R groups, saturated, partially saturated or unsaturated cyclics, nitrogen containing heterocycles, saturated, partially saturated or unsaturated ring structures and straps as defined above.

The "R" groups attached to the carbon atoms of the macrocycle can be in the axial or equatorial position relative to the macrocycle. When the "R" group is other than hydrogen or when two adjacent "R" groups, i.e., on adjacent carbon atoms, together with the carbon atoms to which they are attached form a saturated, partially saturated or unsaturated cyclic or a nitrogen containing heterocycle, or when two R groups on the same carbon atom together with the carbon atom to which they are attached form a saturated, partially saturated or unsaturated ring structure, it is preferred that at least some of the "R" groups are in the equatorial position for reasons of improved activity and stability. This is particularly true when the complex contains more than one "R" group which is not hydrogen.

X, Y and Z represent ligands or chargeneutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). X, Y and Z are independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl

hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), aryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea,alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or systems where one or more of X,Y and Z are independently attached to one or more of the "R" groups, wherein n is an integer from 0 to 3. The preferred ligands from which X, Y and Z are selected include halide, organic acid, nitrate and bicarbonate anions.

Currently, preferred compounds are those wherein at least one, preferably at least two, of the "R" groups represent alkyl, cycloalkylalkyl, aralkyl, aminoalkyl and o-hydroxybenzyl radicals and the remaining R groups represent hydrogen, a saturated, partially saturated or unsaturated cyclic, or a nitrogen containing heterocycle, those wherein at least one, preferably at least two, of $R_1$ or $R'_1$ and $R_2$ or $R'_2$, $R_3$ or $R'_3$ and $R_4$ or $R'_4$, $R_3$ or $R'_3$ and $R_5$ or $R'_5$, $R_4$ or $R'_4$ and $R_5$ or $R'_5$, $R_6$ or $R'_6$ and $R_7$ or $R'_7$, $R_8$ or $R'_8$ and $R_9$ or $R'_9$, and $R_{10}$ or $R'_{10}$ and R or R' together with the carbon atoms to which they are attached represent a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms and all the remaining "R" groups are hydrogen, nitrogen containing heterocycle or alkyl groups, and those wherein at least one, preferably at least two, of R or R' and $R_1$ or $R'_1$, $R_2$ or $R'_2$ and $R_3$ or $R'_3$ or $R_4$ or $R'_4$, $R_4$ or $R'_4$ or or $R'_5$ and $R_6$ or $R'_6$, $R_7$ or $R'_7$ and $R_8$ or $R'_8$, and $R_9$ or $R'_9$ and $R_{10}$ or $R'_{10}$ together with the carbon atoms to which they are attached are bound to form a nitrogen containing heterocycle having 2 to 20 carbon atoms and all the remaining "R" groups are independently selected from hydrogen, saturated, partially saturated or unsaturated cyclic or alkyl groups. As used herein, "R" groups means all of the R groups attached to the carbon atoms of the macrocycle, i.e., R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$.

The commonly accepted mechanism of action of the manganese-based SOD enzymes involves the cycling of the manganese center between the two oxidation states (II,III). See J. V. Bannister, W. H. Bannister, and G. Rotilio, Crit. Rev. Biochem., 22, 111-180 (1987).

$$1) \quad Mn(II) + HO_2^{\cdot} \dashrightarrow Mn(III) + HO_2^{\cdot}$$

$$2) \quad Mn(III) + O_2^{\cdot-} \dashrightarrow Mn(II) + O_2$$

The formal redox potentials for the $O_2/O_2^{\cdot-}$ and $HO_2^{\cdot}/H_2O_2$ couples at pH = 7 are -0.33 v and 0.87 v, respectively. See A. E. G. Cass, in Metalloproteins: Part 1, Metal Proteins with Redox Roles, ed. P. Harrison, P. 121. Verlag Chemie (Weinheim, GDR) (1985). For the above disclosed mechanism, these potentials require that a putative SOD catalyst be able to rapidly undergo oxidation state changes in the range of about -0.33 v to about 0.87 v.

The complexes derived from Mn(II) and the general class of C-substituted [16]ane$N_5$ ligands described herein have been characterized using cyclic voltammetry to measure their redox potential. The C-substituted complexes described herein have oxidations of about +0.7 v (SHE). Coulometry shows that this oxidation is a one-electron process; namely it is the oxidation of the Mn(II) complex to the Mn(III) complex. Thus, for these complexes to function as SOD catalysts, the Mn(III) oxidation state is involved in the catalytic cycle. This means that the Mn(III) complexes of all these ligands are equally competent as SOD catalysts, since it does not matter which form (Mn(II) or Mn(III)) is present when superoxide is present because superoxide will simply reduce Mn(III) to Mn(II) liberating oxygen.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 22 carbon atoms, preferably from about 1 to about 18 carbon atoms, and most preferably from about 1 to about 12 carbon atoms. Examples of such radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, octadecyl and eicosyl. The term "alkenyl", alone or in combination, means an alkyl radical having one or

more double bonds. Examples of such alkenyl radicals include, but are not limited to, ethenyl, propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl, iso-butylenyl, cis-2-pentenyl, trans-2-pentenyl, 3-methyl-1-butenyl, 2,3-dimethyl-2-butenyl, 1-pentenyl, 1-hexenyl, 1-octenyl, decenyl, dodecenyl, tetradecenyl, hexadecenyl, cis- and trans- 9-octadecenyl, 1,3-pentadienyl, 2,4-pentadienyl, 2,3-pentadienyl, 1,3-hexadienyl, 2,4-hexadienyl, 5,8,11,14-eicosatetraenyl, and 9,12,15-octadecatrienyl. The term "alkynyl", alone or in combination, means an alkyl radical having one or more triple bonds. Examples of such alkynyl groups include, but are not limited to, ethynyl, propynyl (propargyl), 1-butynyl, 1-octynyl, 9-octadecynyl, 1,3-pentadiynyl, 2,4-pentadiynyl, 1,3-hexadiynyl, and 2,4-hexadiynyl. The term "cycloalkyl", alone or in combination means a cycloalkyl radical containing from 3 to about 10, preferably from 3 to about 8, and most preferably from 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and perhydronaphthyl. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of cycloalkylalkyl radicals include, but are not limited to, cyclohexylmethyl, cyclopentylmethyl, (4-isopropylcyclohexyl) methyl, (4-t-butyl-cyclohexyl)methyl, 3-cyclohexylpropyl, 2-cyclohexylmethylpentyl, 3-cyclopentylmethylhexyl, 1-(4-neopentylcyclohexyl)methylhexyl, and 1-(4-isopropylcyclohexyl)methylheptyl. The term "cycloalkylcycloalkyl" means a cycloalkyl radical as defined above which is substituted by another cycloalkyl radical as defined above. Examples of cycloalkylcycloalkyl radicals include, but are not limited to, cyclohexylcyclopentyl and cyclohexylcyclohexyl. The term "cycloalkenyl", alone or in combination, means a cycloalkyl radical having one or more double bonds. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl. The term "cycloalkenylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkenyl radical as defined above. Examples of cycloalkenylalkyl radicals include, but are not limited to, 2-cyclohexen-1-ylmethyl, 1-cyclopenten-1-ylmethyl, 2-(1-cyclohexen-1-yl)ethyl, 3-(1-cyclopenten-1-yl)propyl, 1-(1-cyclohexen-1-ylmethyl)pentyl, 1-(1-cyclopenten-1-yl)hexyl, 6-(1-cyclohexen-1-yl)hexyl, 1-(1-cyclopenten-1-yl)nonyl and 1-(1-cyclohexen-1-yl)nonyl. The terms "alkylcycloalkyl" and "alkenylcycloalkyl" mean a cycloalkyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkyl and alkenylcycloalkyl radicals include, but are not limited to, 2-ethylcyclobutyl, 1-methylcyclopentyl, 1-hexylcyclopentyl, 1-methylcyclohexyl, 1-(9-octadecenyl)cyclopentyl and 1-(9-octadecenyl)cyclohexyl. The terms "alkylcycloalkenyl" and "alkenylcycloalkenyl" means a cycloalkenyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkenyl and alkenylcycloalkenyl radicals include, but are not limited to, 1-methyl-2-cyclopentyl, 1-hexyl-2-cyclopentenyl, 1-ethyl-2-cyclohexenyl, 1-butyl-2-cyclohexenyl, 1-(9-octadecenyl)-2-cyclohexenyl and 1-(2-pentenyl)-2-cyclohexenyl. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, cycloalkyl, cycloalkenyl, aryl, heterocycle, alkoxyaryl, alkaryl, alkoxy, halogen, hydroxy, amine, cyano, nitro, alkylthio, phenoxy, ether, trifluoromethyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl or cycloalkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl, and the like. The term "heterocyclic" means ring structures containing at least one other kind of atom, in addition to carbon, in the ring. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. Examples of heterocyclics include, but are not limited to, pyrrolidinyl, piperidyl, imidazolidinyl, tetrahydrofuryl, tetrahydrothienyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, benzoxadiazolyl, benzothiadiazolyl, triazolyl and tetrazolyl groups. The term "saturated, partially saturated or unsaturated cyclic" means fused ring structures in which 2 carbons of the ring are also part of the sixteen-membered macrocyclic ligand. The ring structure can contain 3 to 20 carbon atoms, preferably 5 to 10 carbon atoms, and can also contain one or more other kinds of atoms in addition to carbon. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. The ring structure can also contain more than one ring. The term "saturated, partially saturated or unsaturated ring structure" means a ring structure in which one carbon of the ring is also part of the sixteen-membered macrocyclic ligand. The ring structure can contain 3 to 20, preferably 5 to 10, carbon atoms and can also contain nitrogen, oxygen and/or sulfur atoms. The term "nitrogen containing heterocycle" means ring structures in which 2 carbons and a nitrogen of the ring are also part of the sixteen-membered macrocyclic ligand. The ring structure can contain 2 to 20, preferably 4 to 10, carbon atoms, can be partially or fully unsaturated or saturated and can also contain nitrogen, oxygen and/or sulfur atoms in the portion of the ring which is not also part of the sixteen-membered macrocyclic ligand. The term "organic acid anion" refers to carboxylic acid anions having from about 1 to about 18 carbon atoms. The term "halide" means chloride or bromide. Any of the R groups defined above can optionally carry one or more substituents selected from halogen, amine, hydroxy, cyano, nitro, trifluoromethyl, and the like.

The macrocyclic ligands useful in the complex of the present invention wherein all of the R groups are H can be prepared according to the general synthetic scheme A set forth below utilizing methods known in the art for the preparation of certain intermediates and certain ligands. See for example Richman et al., J. Am. *Chem. Soc.*, 96, 2268, (1974); Atkins et al. *Org. Synth.*, 58, 86 (1978); and EP 287465. Thus in scheme A a tetraazaalkane is tosylated in a suitable solvent system to produce the corresponding tetratosyl derivative. Such derivative is then treated with a suitable

base to produce the corresponding disulfonamide anion. This disulfonamide anion is then cycloalkylated with a di-O-tosylated mono-N-tosylated azaalkane diol to produce the pentatosylpentaazacycloalkane. The tosyl groups are then removed and the resulting compound is reacted with a manganese (II) compound under anaerobic conditions to form the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention, wherein $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$ and $R'_5$ can be H or any functionality previously described, can also be prepared according to the general procedure shown in scheme B set forth below. Thus, a 1,3-diaminopropanediamine is converted to its ditosyl derivative in a suitable solvent. This ditosyl derivative is then converted to its disulfonamide anion with a suitable base. Additionally, the triazaalkane is converted to its tritosyl derivative in a similar manner. This tritosyl derivative is then reacted with ethylene carbonate and a suitable base to afford the tri-N-tosyl diol derivative. This diol is then converted to the tri-N-tosyl di-O-tosyl derivative in a suitable solvent. The disulfonamide anion is then cycloalkylated with the tri-N-tosyl di-O-tosyl derivative. The tosyl groups are removed and the resulting compound is reacted with a manganese (II) compound under anaerobic conditions to form the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention, wherein $R_4$ and $R'_4$ can be H or any functionality previously described and P can be H or tosyl, can be prepared according to scheme C set forth below. The pentaazaalkane is cyclocondensed with a malonyl dichloride or diester in a suitable solvent with a suitable base. The resulting cyclic diamide is then reduced and detosylated to the desired ligand system with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention, wherein $R_3$, $R'_3$ and $R_4$ can be H or any functionality previously described and P can be H or tosyl, can be prepared according to scheme D set forth below. The pentaazaalkane is cyclocondensed with an acrylate or acryloyl chloride in a suitable solvent using a suitable base. The resulting cyclic amide is then reduced and detosylated with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands containing pendant phenols useful in the complexes of the present invention, wherein $R_3$, $R_4$, $R_{11}$, $R_{12}$, $R_{13}$, and $R_{14}$ can be H or any functionality previously described and P can be H or tosyl, can be prepared according to scheme E set forth below. The pentaazaalkane is cyclocondensed with a coumarin derivative to afford the macrocyclic amide containing a pendant phenol. The resulting cyclic amide is then reduced and detosylated with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention can also be prepared according to scheme F, set forth below. The complete possible substitution for Scheme F has been fully illustrated in this method. The other methods (Schemes A through E and G through P) can also have further R substitutions than those shown in the respective methods and such substitutions would be readily apparent to those skilled in the art. Additionally $R_4$ and/or $R'_4$ can be connected to themselves (generating a spiro ring substituent on the trimethylene bridge) and/or any other R group on the macrocyclic ring (R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$) to generate "strapped" macrobicyclic or macrotricyclic ligand systems. In scheme F the pentaazaalkane is cycloalkylated with a 1,3-dihalo or di-O-tosyl propane derivative. The resulting macrocycle is detosylated and reacted with a manganese (II) compound under anaerobic conditions to form the corresponding polysubstituted manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, and $R'_5$ can be H or any other functionality previously described can also be prepared according to scheme G set forth below. The 1,3-diaminopropane derivative is di-acylated with chloroacetyl chloride. The resulting bis-chloroacetamide is then cycloalkylated with either the triazaalkane or the di-sulfonamide anion of the corresponding tri-N-tosyl triazaalkane. The cyclic diamides are the reduced and detosylated (if necessary) with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, R and R' can be H or any other functionality previously described and which also contain a cis- or trans-fused cyclohexyl ring can be prepared according to scheme H set forth below (a system incorporating a trans-fused cyclohexyl ring has been illustrated). The bis-chloroacetamide is cycloalkylated with the triazaalkane or the bis-N-tosyl triazaalkane. The resulting cyclic triamides are then reduced and detosylated (if necessary) with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex. The bis-N-tosyl triazaalkane described above an be prepared by monotosylation of diaminocyclohexane followed by coupling with any natural or unnatural amino acid derivative under standard conditions. The Boc group is then removed and the free amine is tosylated. The triazaalkane also described above can be prepared by monosilylation of diaminocyclohexane followed by coupling with any natural or unnatural amino acid deri-

vated under standard conditions. The Boc and the silyl groups can then be removed by treatment with HCl in dioxane followed by free base generation under suitable conditions.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_3$, $R'_3$, $R_4$, and $R'_4$ can be H or any other functionality previously described and which also contain two cis- and/or trans-fused cyclohexyl rings (trans for illustration), can be prepared according to scheme I set forth below. The monosilylated diaminocyclohexane derivative is coupled with any β-amino acid derivative under standard conditions. The Boc and silyl groups are then removed and the resulting triazaalkane is cycloalkylated with the bis-chloroacetamide. The resulting cyclic triamide is then reduced with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex containing substitution and two fused cyclohexyl rings.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_4$ and $R'_4$ can be H or any other functionality previously described and two cis- or trans-fused diaminocyclohexane rings (trans for illustration) can be prepared according to scheme J set forth below. N-tosyliminodiacetic acid is converted to the diacid chloride by reaction with thionyl chloride or oxalyl chloride. The diacid chloride is the reacted with excess diaminocyclohexane to afford the diamino diamide derivative. This derivative is then cyclocondensed with a malonyl dichloride or diester to afford the macrocyclic tetraamide. This derivative is then reduced and detosylated with lithium aluminum hydride. This type of ligand is reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex containing substitution and two fused cyclohexyl rings.

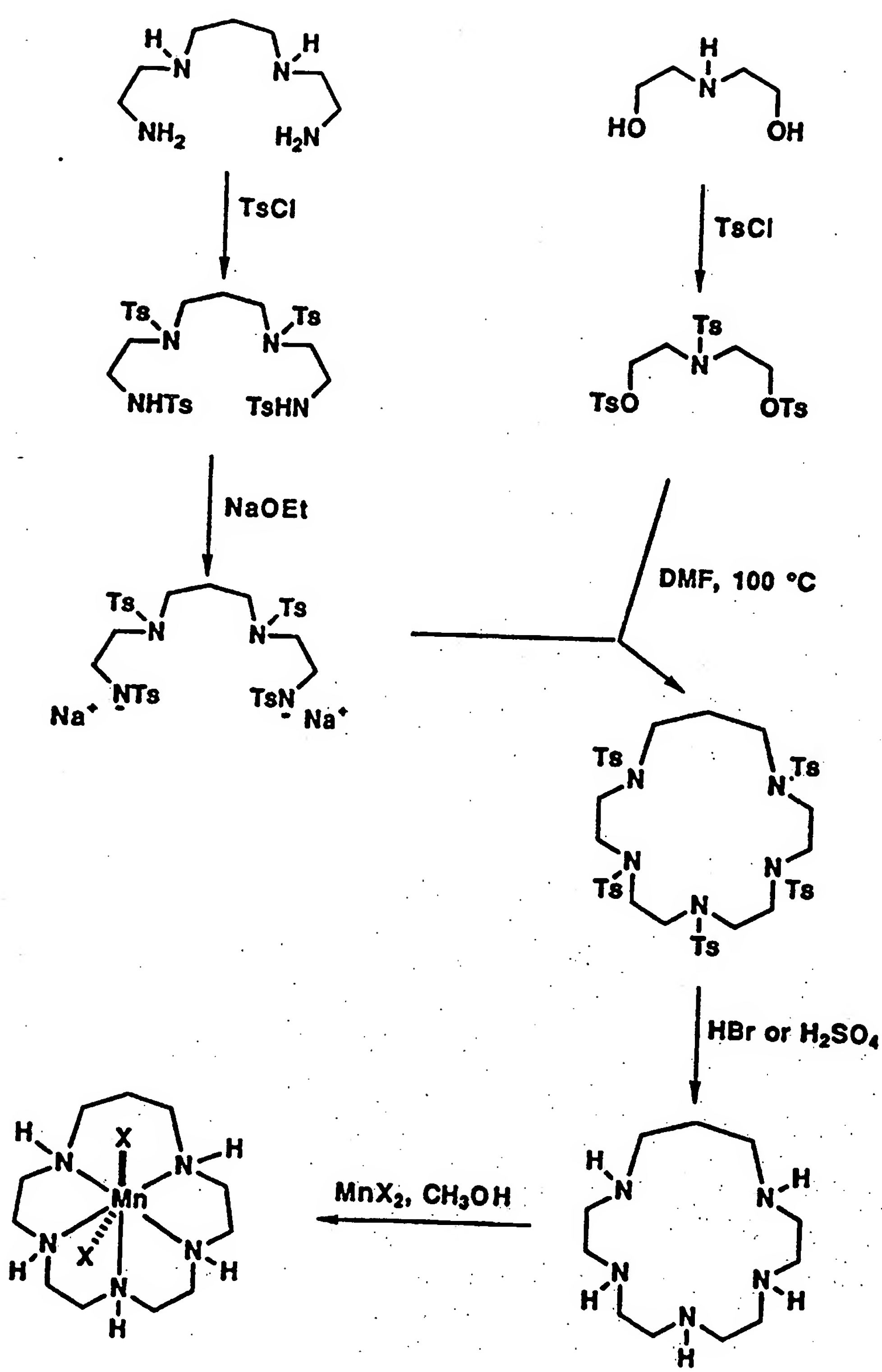
The macrocyclic ligands useful in the complexes of the present invention wherein $R_1$, $R'_1$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_6$, $R'_6$, $R_8$, $R'_8$, $R_{10}$ and $R'_{10}$ can be H or any functionality previously described can be prepared according to the general peptide method outlined in scheme K set forth below. The procedures for preparing the cyclic peptide precursors from the corresponding linear peptides are the same or significant modifications of methods known in the art. See, for example, Veber, D.F. et al., *J. Org. Chem.*, 44, 3101 (1979) and EP-A-0,524,161. The starting pentapeptide in scheme K can be prepared by standard solution or solid-phase synthesis and must incorporate one β-amino acid. This compound is then converted to the corresponding cyclic peptide by treatment with diphenylphosphoryl azide. The cyclic peptide is then reduced with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_1$, $R'_1$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_{10}$ and $R'_{10}$ can be H or any functionality previously described and which also contain one cis- or trans-fused cyclohexane ring can be prepared by scheme L set forth below. Mono-N-tosyl diaminocyclohexane is converted to the Boc derivative under standard conditions. The tosylamide is then alkylated with methyl bromoacetate using a suitable base. The resulting pseudo-dipeptide methyl ester is saponified to the free acid which is coupled with any natural or unnatural amino acid under standard conditions. The Boc group is then removed and the amino group of the pseudo-tripeptide is then coupled to any N-Boc protected β-amino acid derivative under standard conditions. The Boc group is then removed and the free amino group is then coupled to any natural or unnatural amino acid derivative. The resulting pseudopentapeptide is then deprotected with HCl/acetic acid and cyclized by treatment with diphenylphosphoryl azide. The cyclic pseudo-peptide is then reduced and detosylated with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex containing a fused cyclohexane ring.

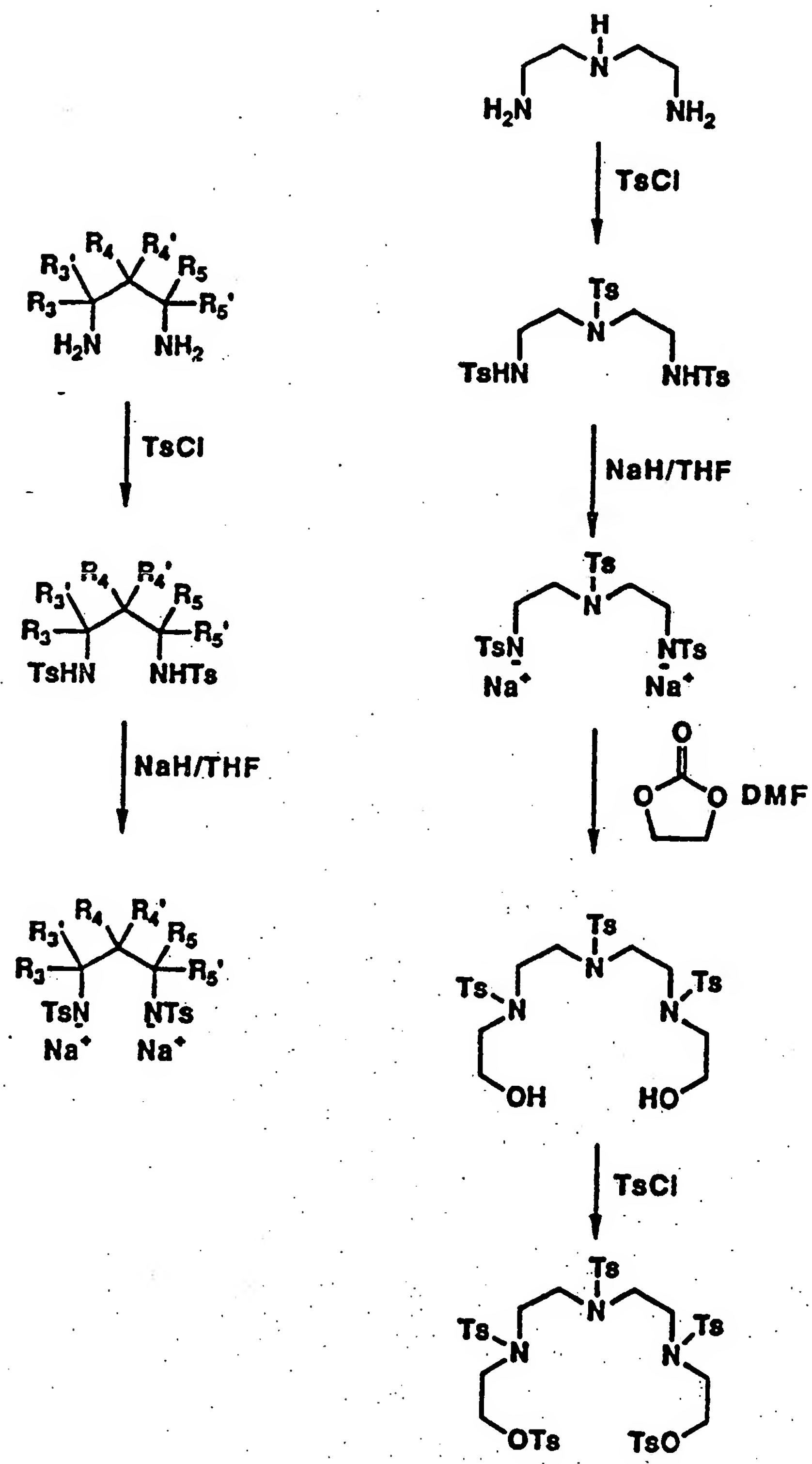
The macrocyclic ligands useful in the complexes of the present invention, wherein $R_3$, $R'_3$, $R_4$, and $R'_4$ can be H or any other functionality previously described and which contain two cis- and/ or trans- fused cyclohexane ring can be prepared according to scheme M set forth below. The cyclohexyl pseudo-dipeptide is saponified to the free acid. Another amount of the cyclohexyl pseudo-dipeptide is treated with TFA to remove the Boc. These two derivatives are then coupled together under standard conditions. The Boc is then removed from the resulting pseudo-tetrapeptide and the free amino group is coupled to any Boc protected β-amino acid derivative under standard conditions. The pseudopentapeptide is then deprotected and cyclized. The cyclic pseudo-peptide is reduced and detosylated with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) substituted pentaaza-cycloalkane complex containing two fused cyclohexanes.

The macrocyclic ligands useful in the complexes of the present invention wherein $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_{11}$, $R_{12}$, $R_{13}$ and $R_{14}$ can be H or any functionality previously described and can contain 2(aminomethyl)cyclohexylamine or 2-(aminomethyl)aniline substitution can be prepared by the general diacid dichloride method previously described and outlined in schemes N, O and P. See, for example, EP-A-0,524,161, which is incorporated by reference herein. The tri-N-tosyl triazaalkane is alkylated with methyl chloroacetate using a suitable base. The resulting diester is saponified and converted to the diacid chloride under standard conditions. The diacid chloride is then cyclocondensed with the 1,3-diamine using a suitable solvent and base. The resulting macrocyclic diamide is reduced and detosylated with lithium aluminum hydride. This type of ligand is then reacted with a manganese (II) compound under anaerobic conditions to afford the corresponding manganese (II) pentaazacycloalkane complex.

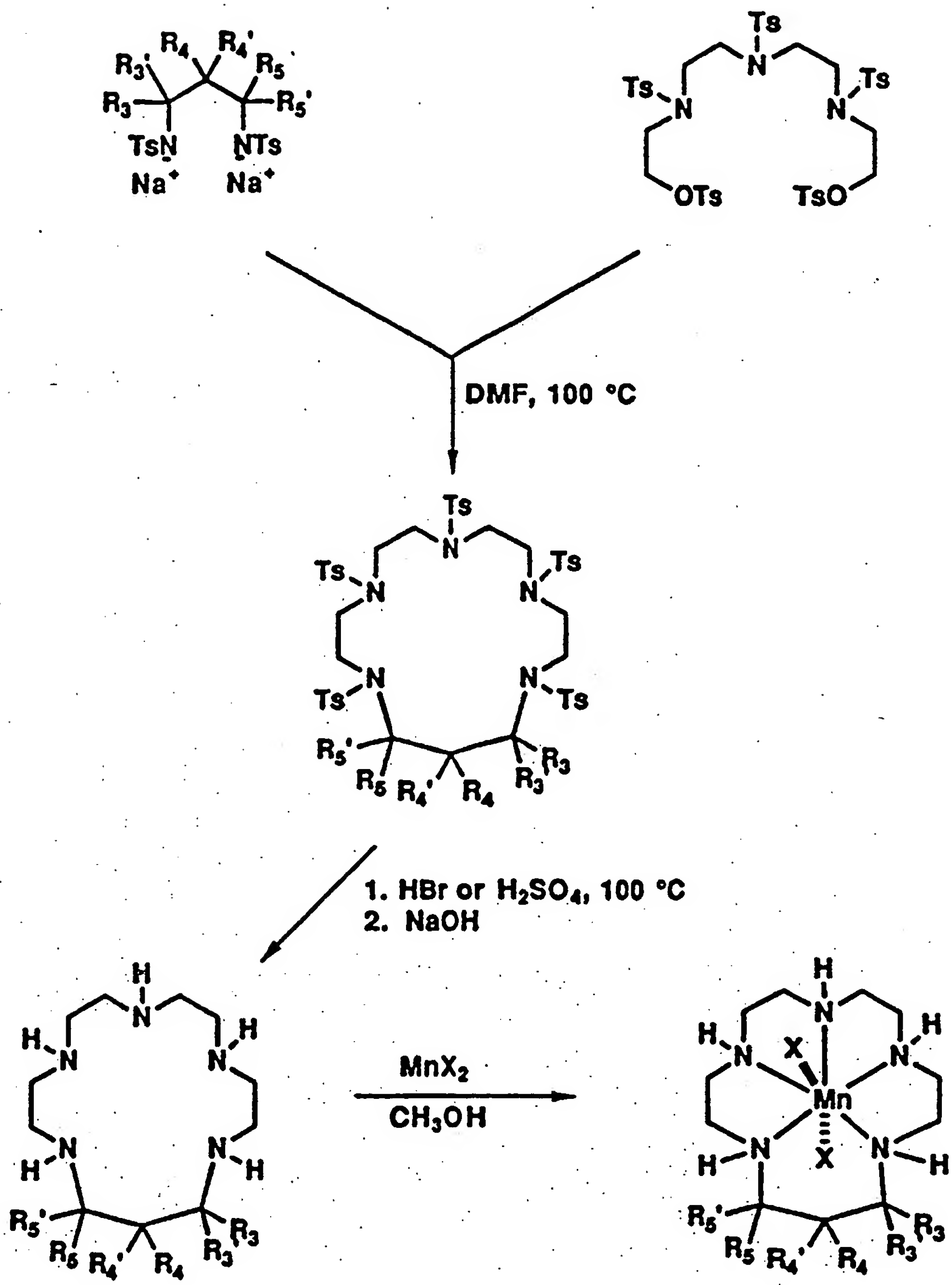
**Scheme A**



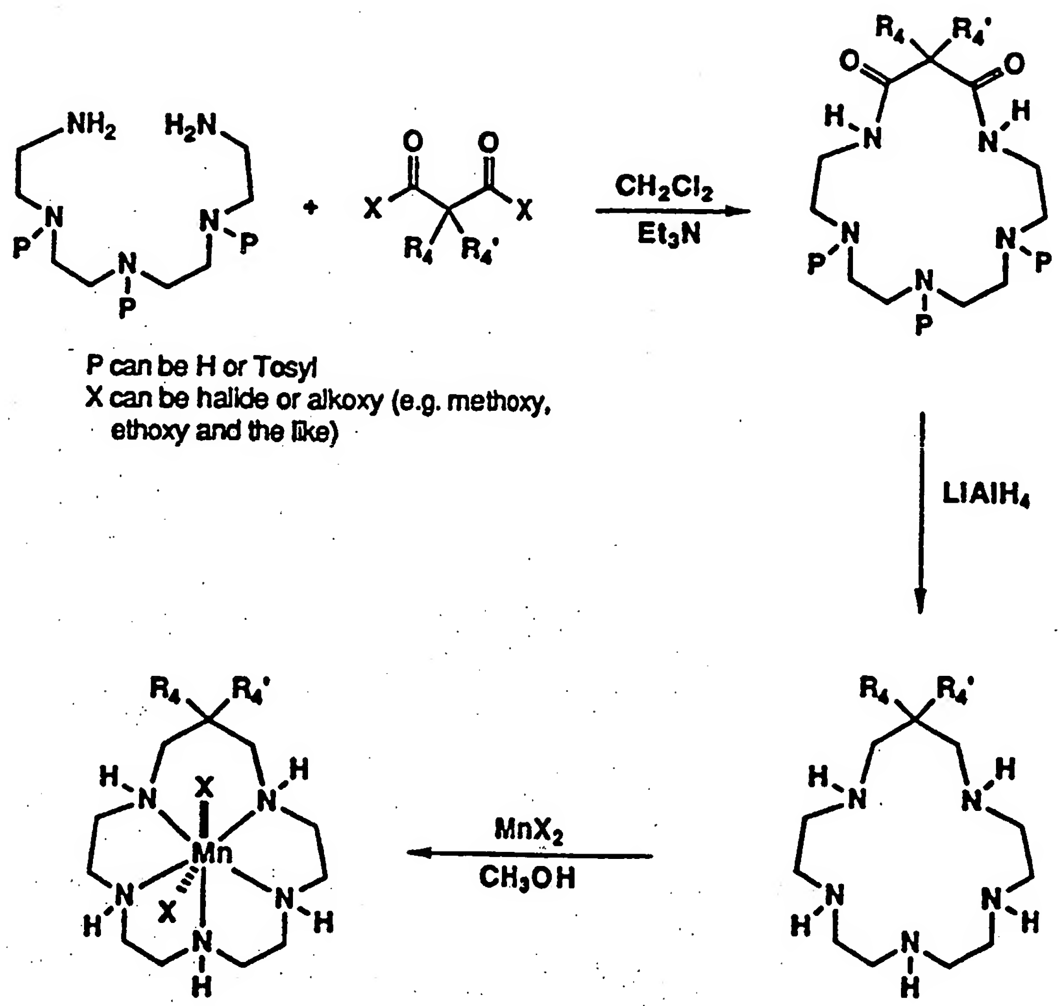
Scheme B (General Substituted 1,3-propane diamines)



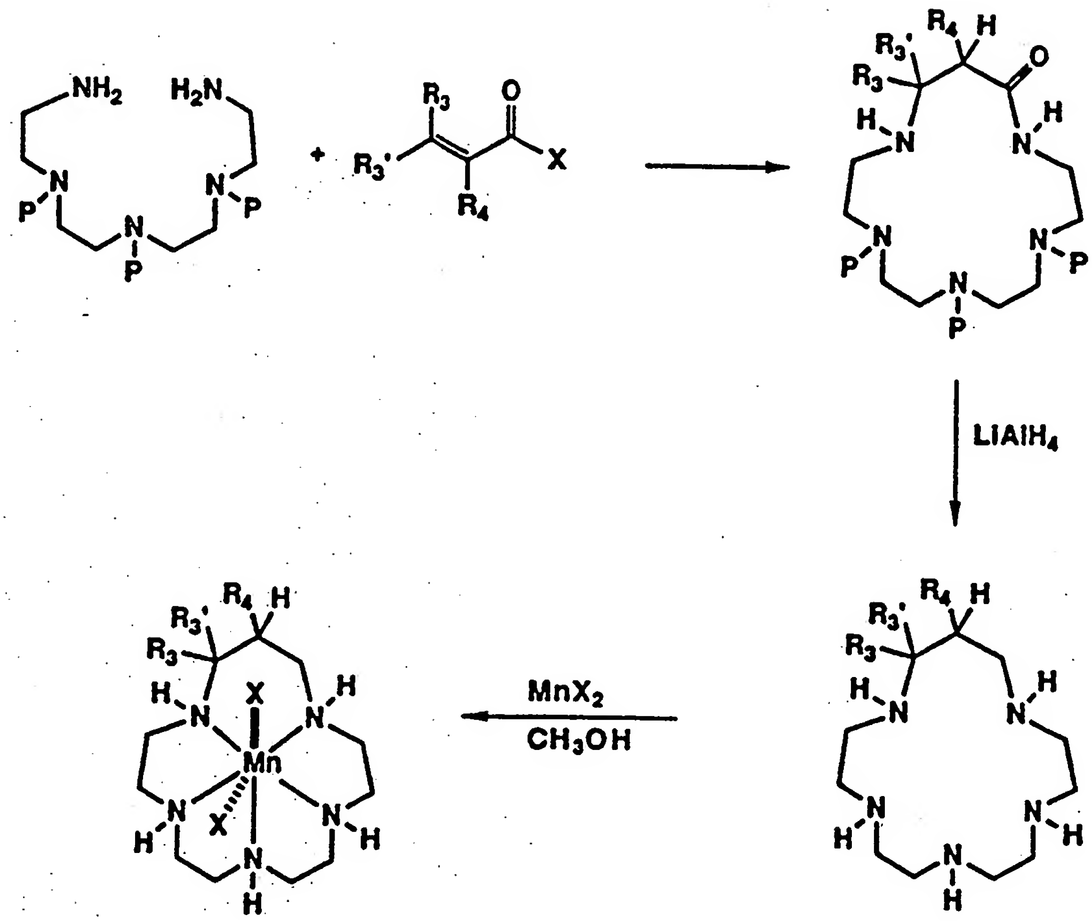
Scheme B (Cont'd)



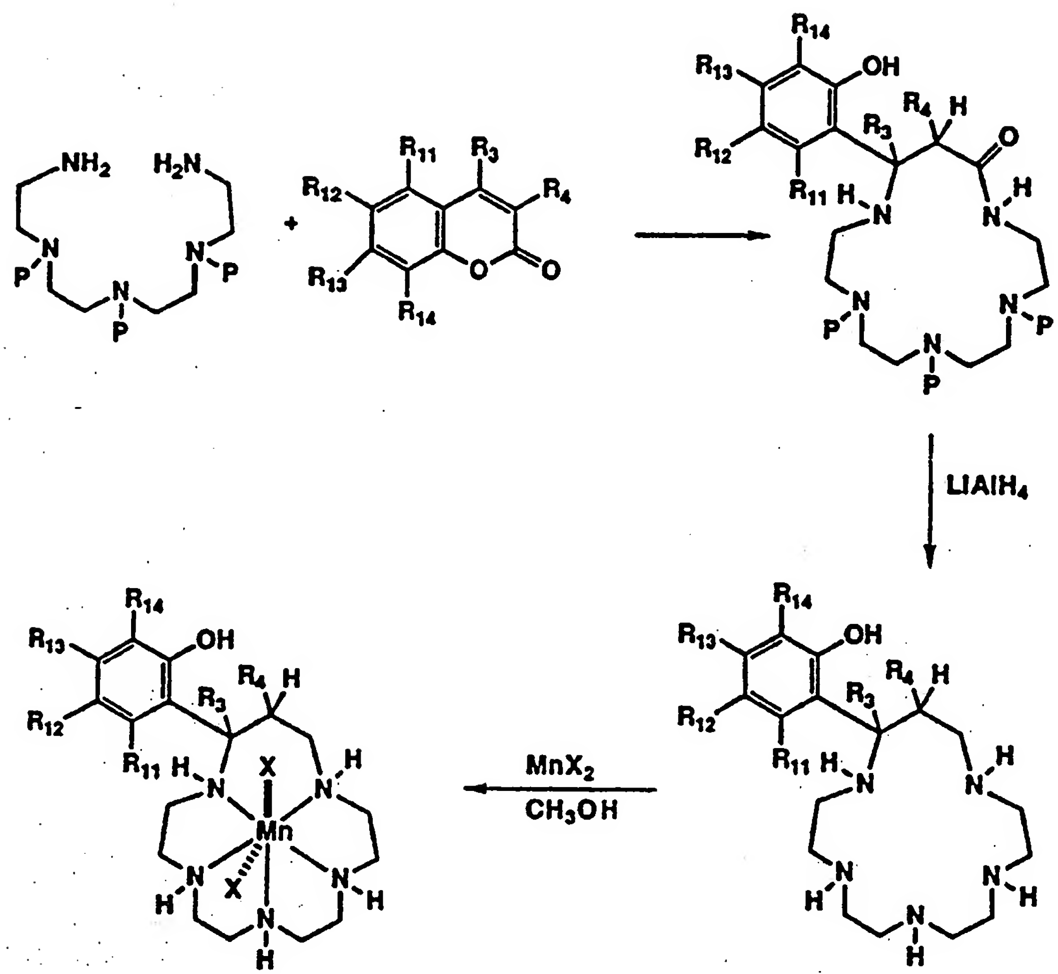
Scheme C (Malonates)



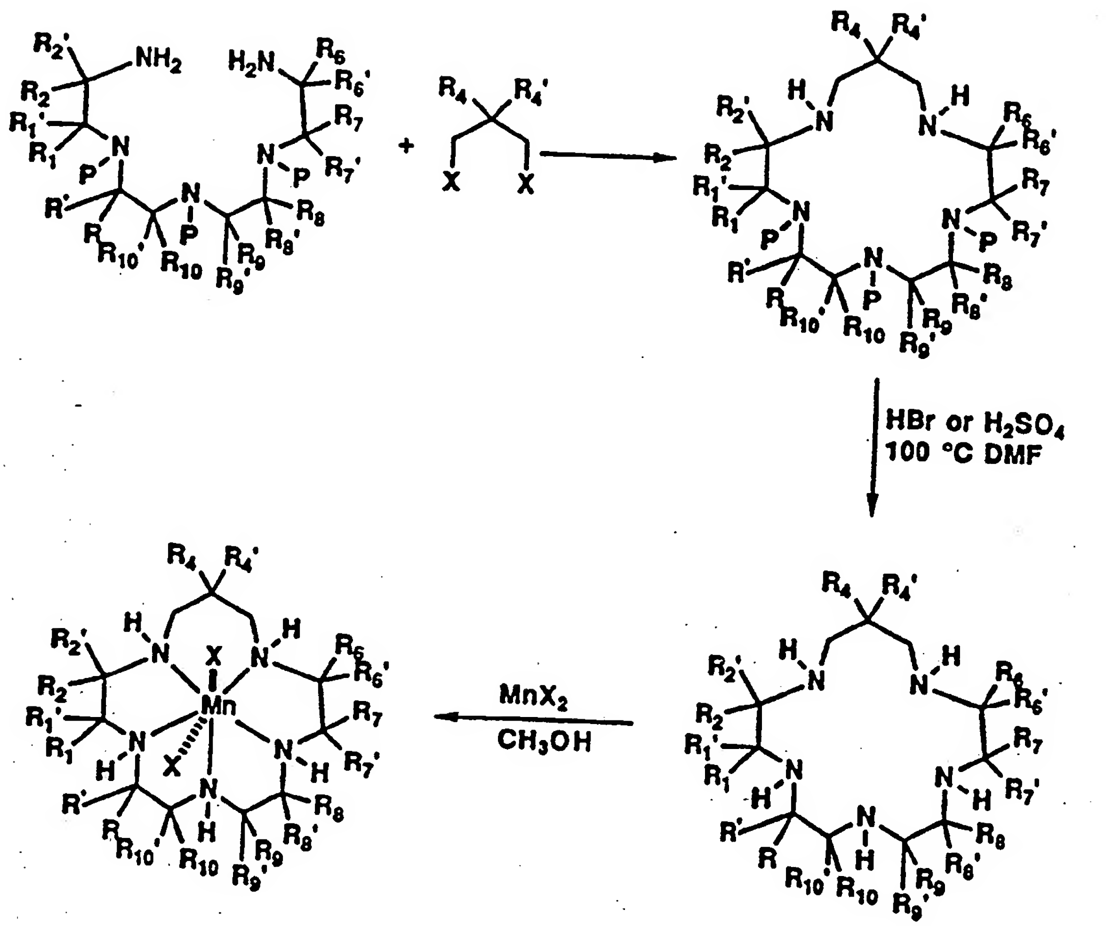
Scheme D (Acrylates)



Scheme E (Coumarins)

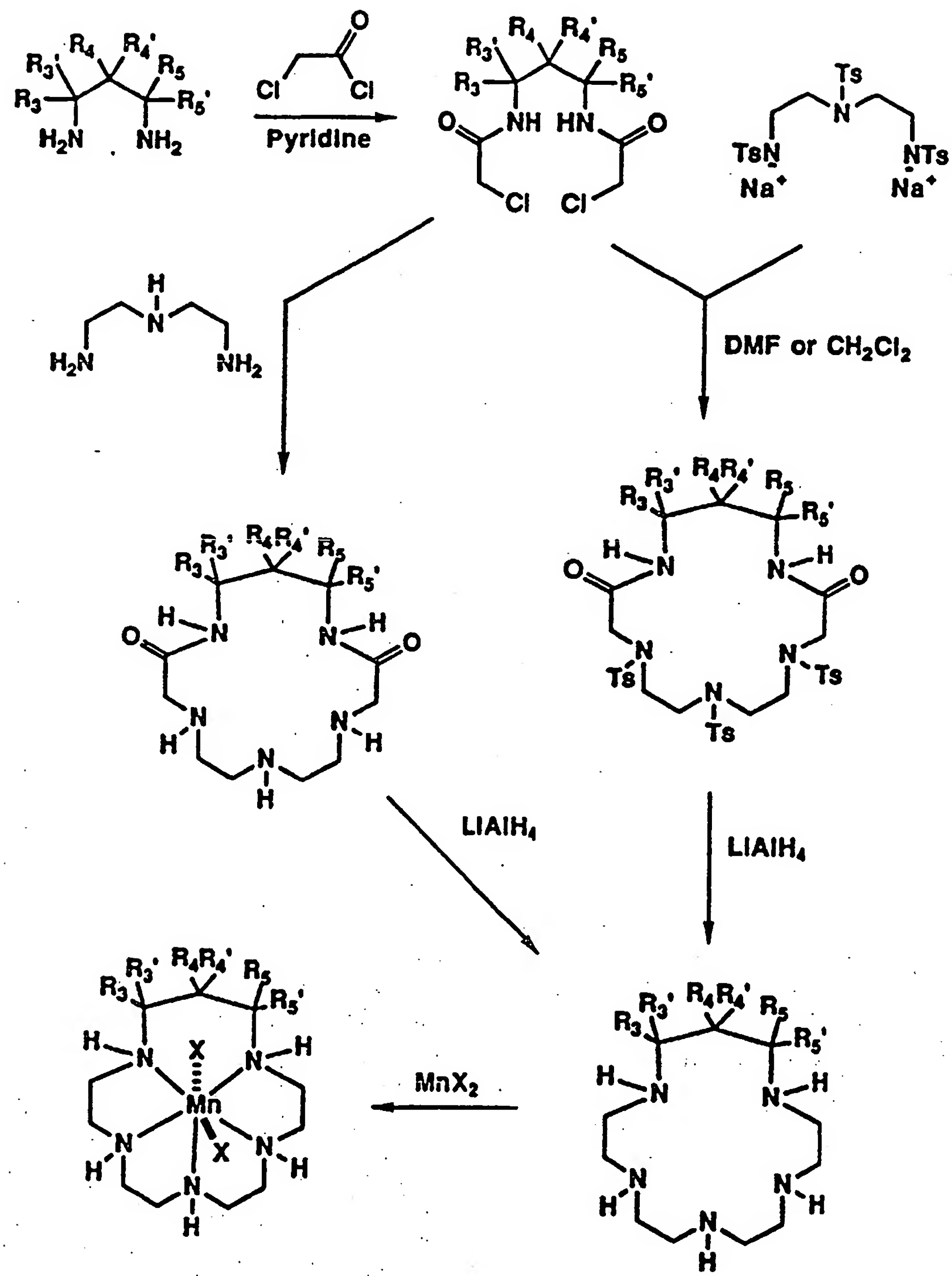


Scheme F (Alkylations)

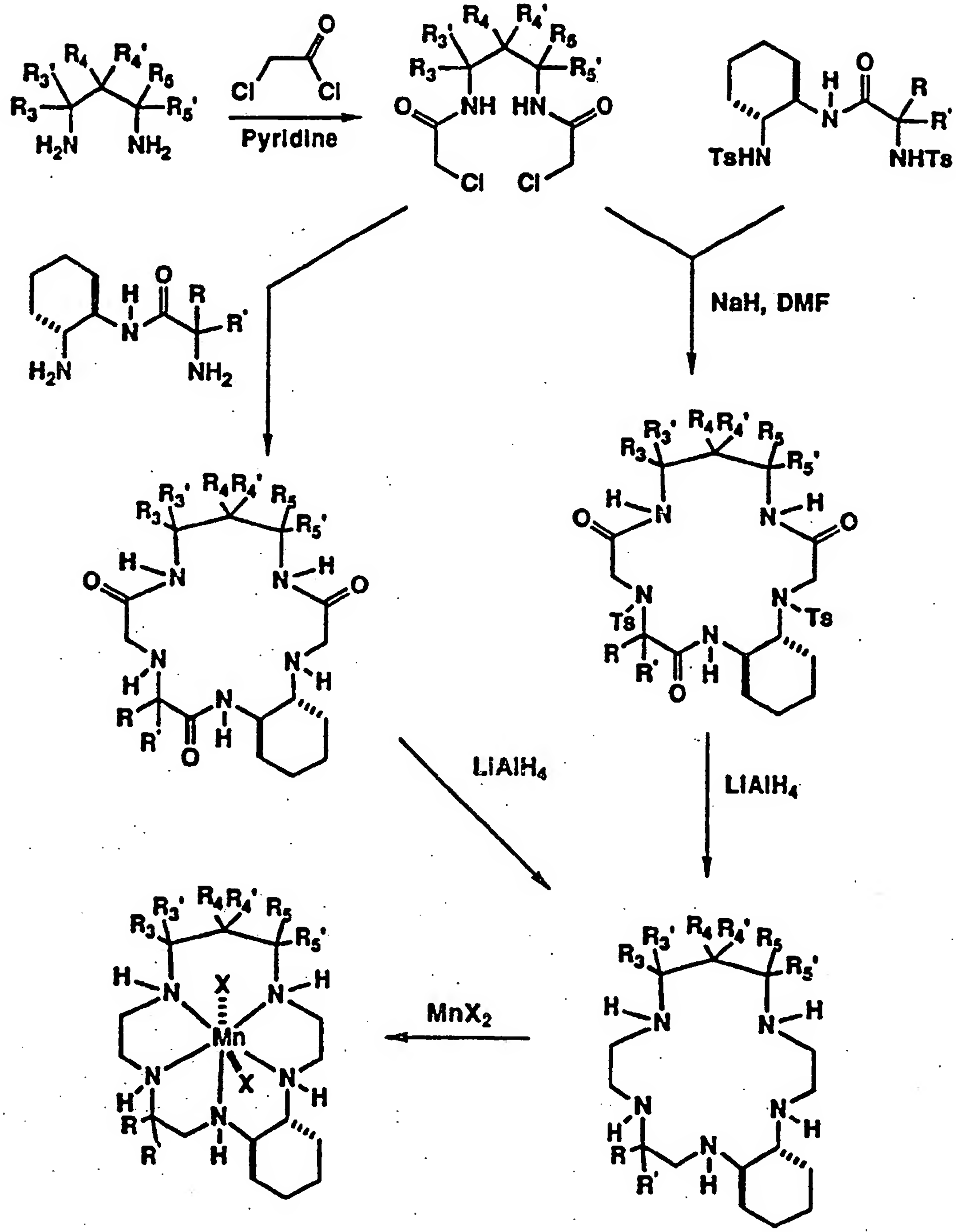



Additionally $R_4$ and/or $R'_4$ can be connected to themselves (generating a spiro ring system on the trimethylene bridge) and/or any other R group on the ring (R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$) to generate "strapped" macrobicyclic or macrotricyclic ligand systems.

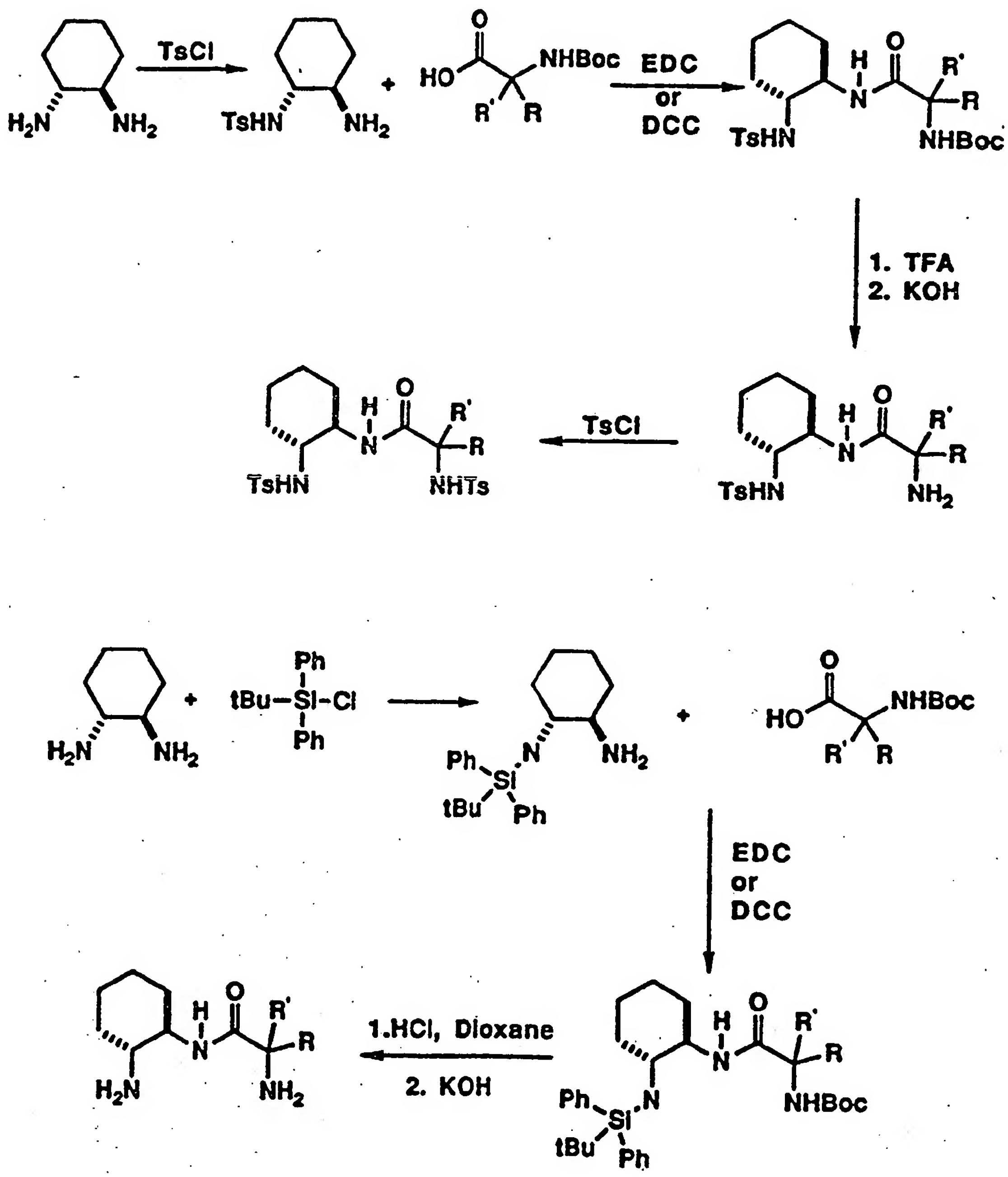
Scheme G



Scheme H (1,2-Diaminocyclohexane substitution)

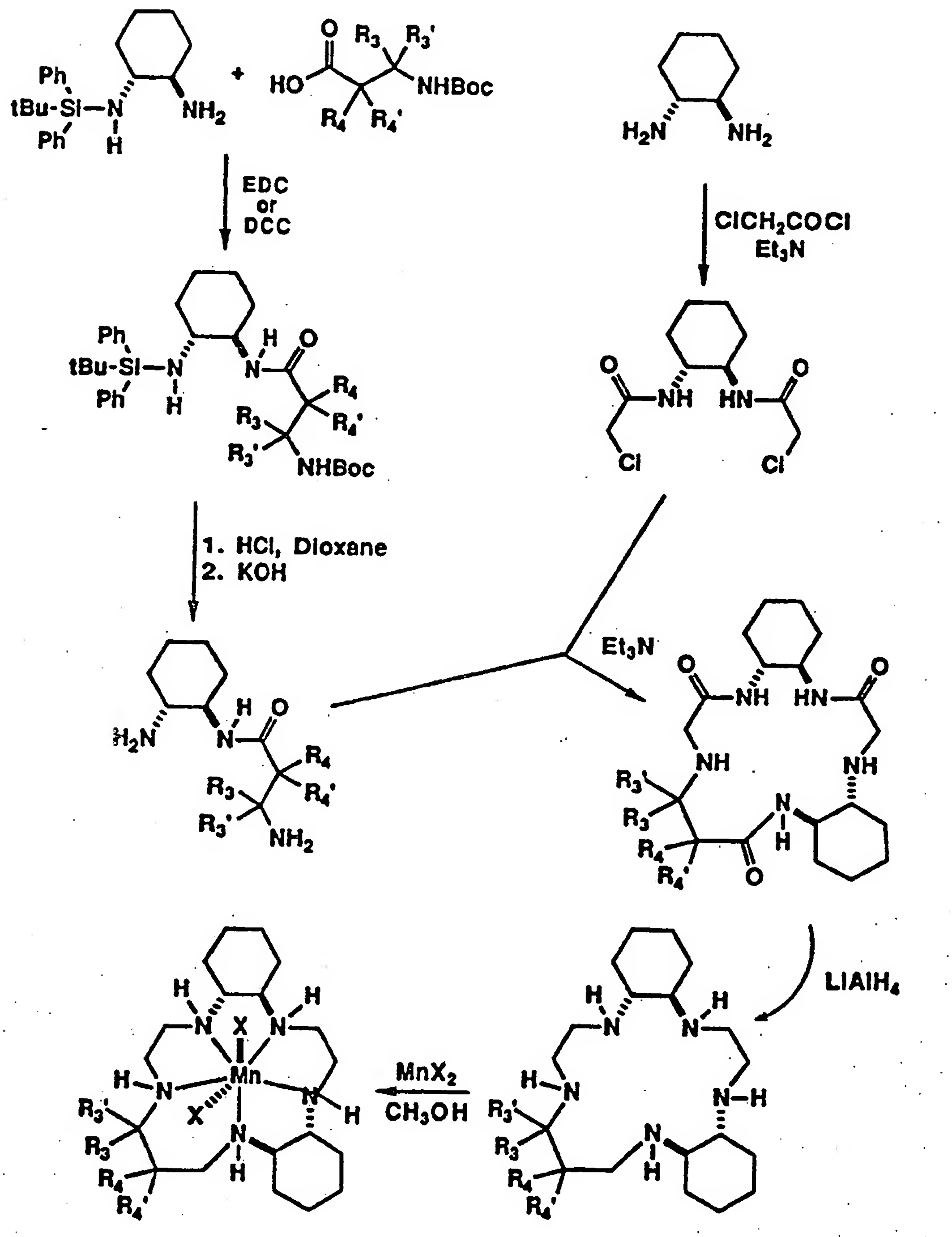


Scheme H (Cont'd)

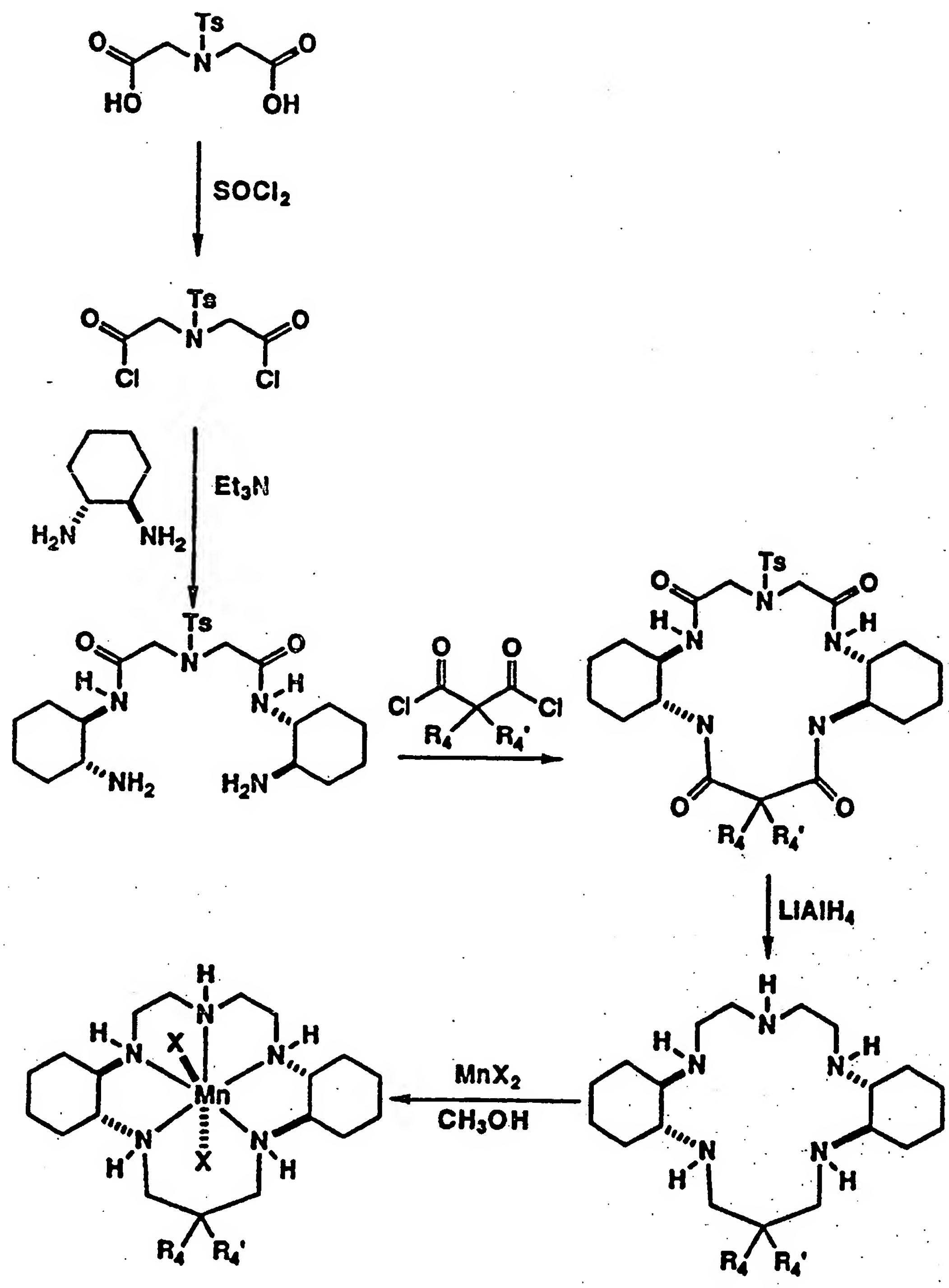


Scheme I

(Bis-1,2-Diaminocyclohexane substitution, $\beta$-amino acid chemistry)

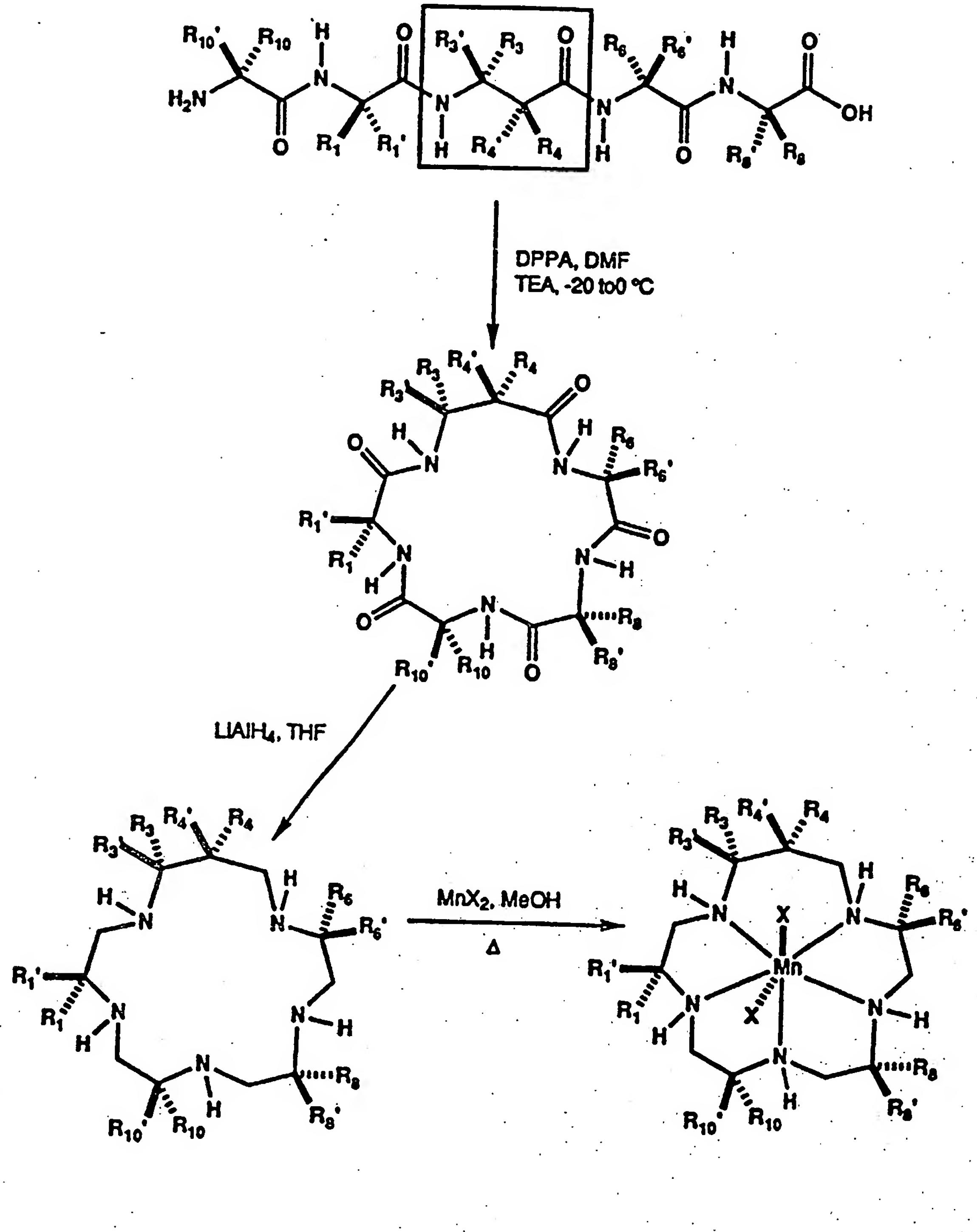


Scheme J (Bis-1,2-Diaminocyclohexane substitution)



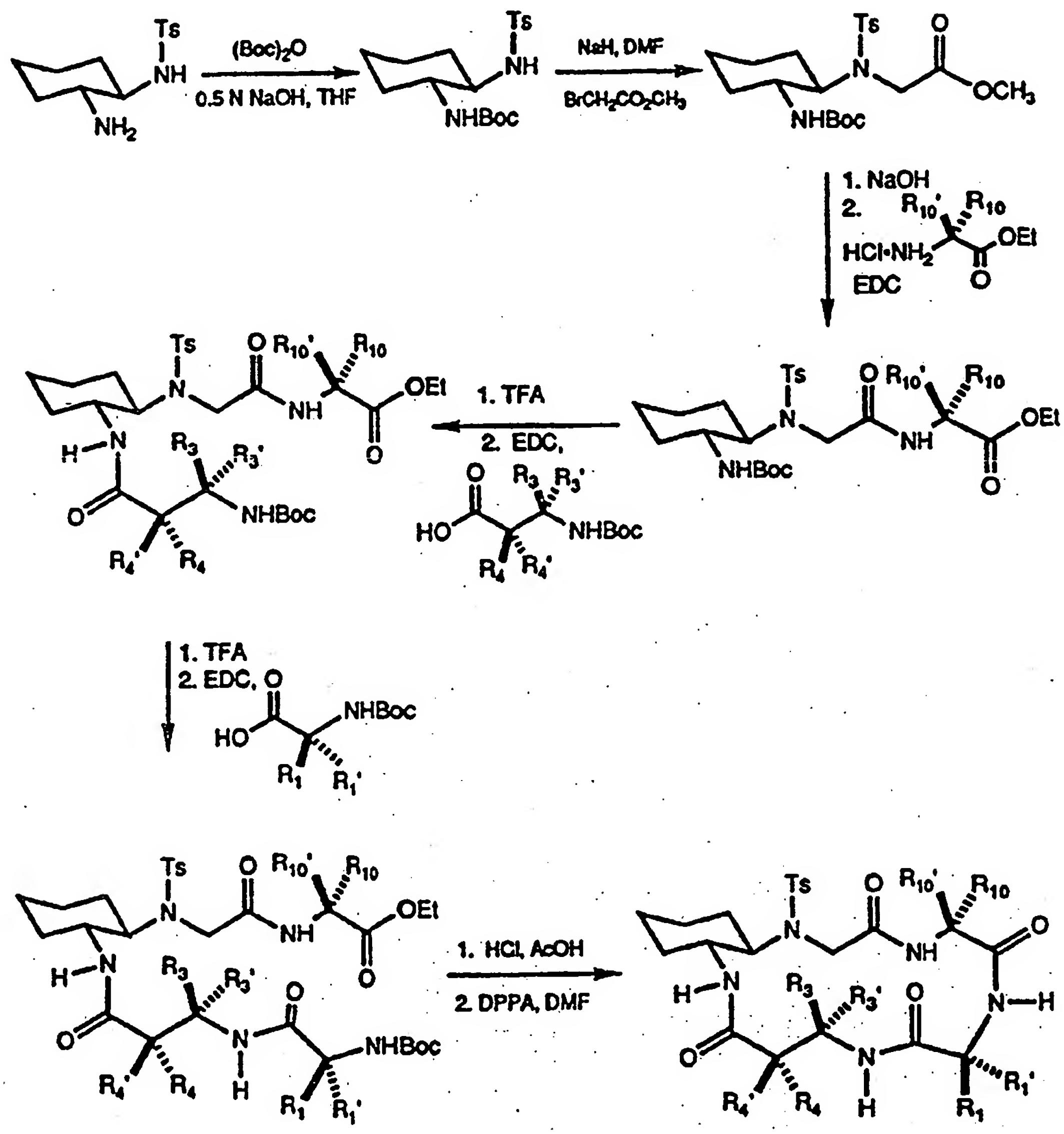
**Scheme K**

**(Cyclic peptide approach with one β-amino acid residue)**

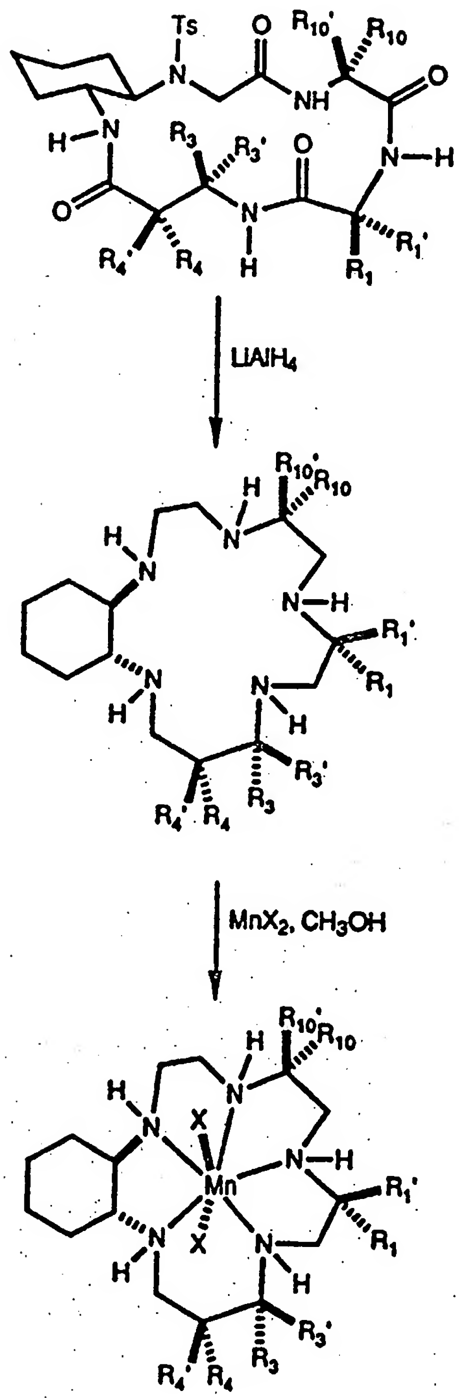


**Scheme L**

**(1,2-diaminocyclohexane pseudo-peptides with β-amino acids)**

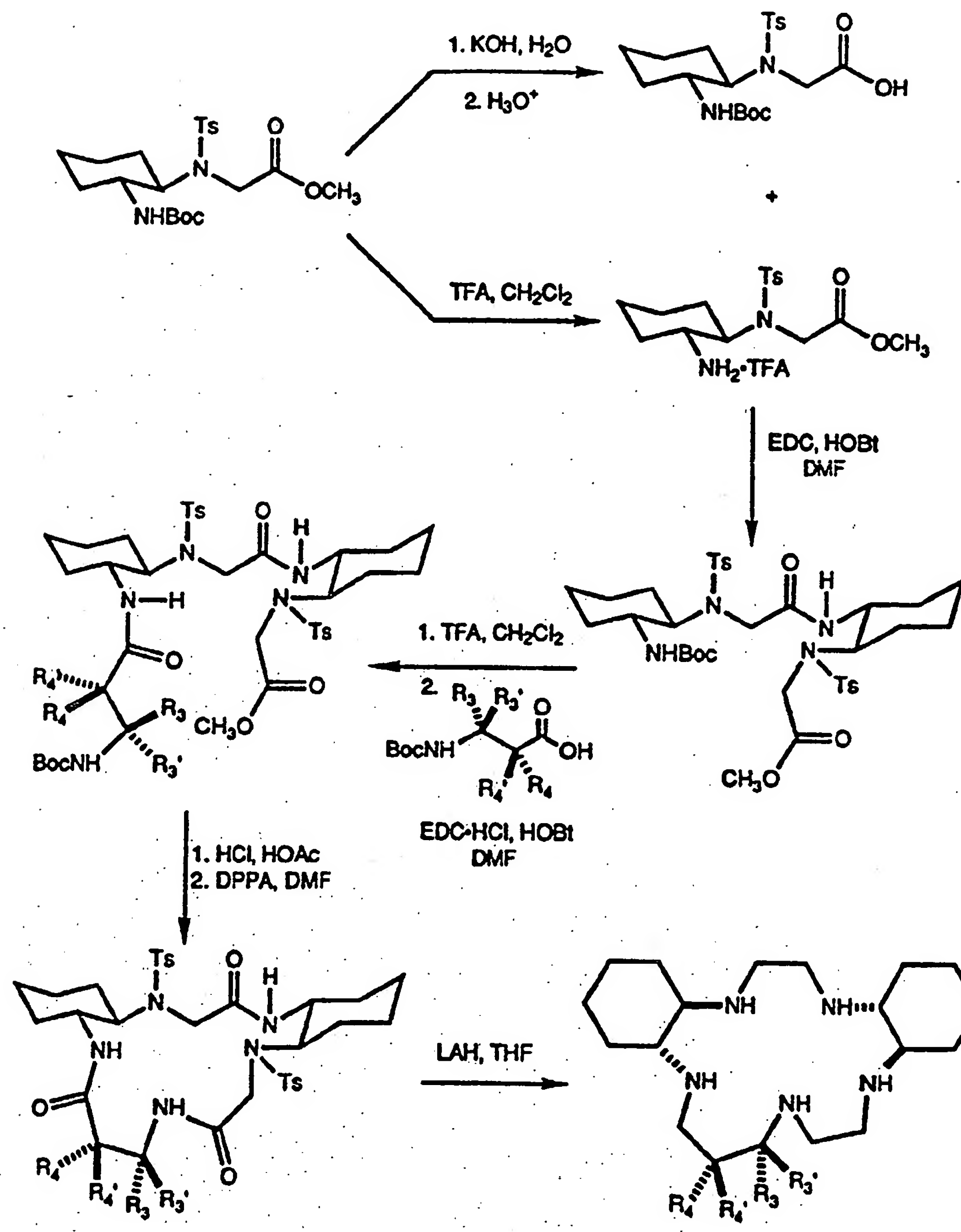


Scheme L (Cont'd)

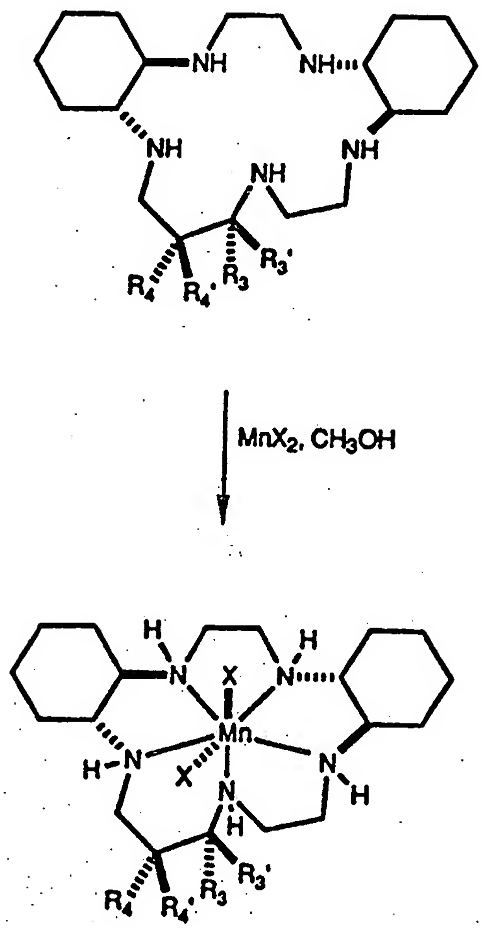


**Scheme M**

**(Bis-1,2-cyclohexanediamino with β-amino acids)**

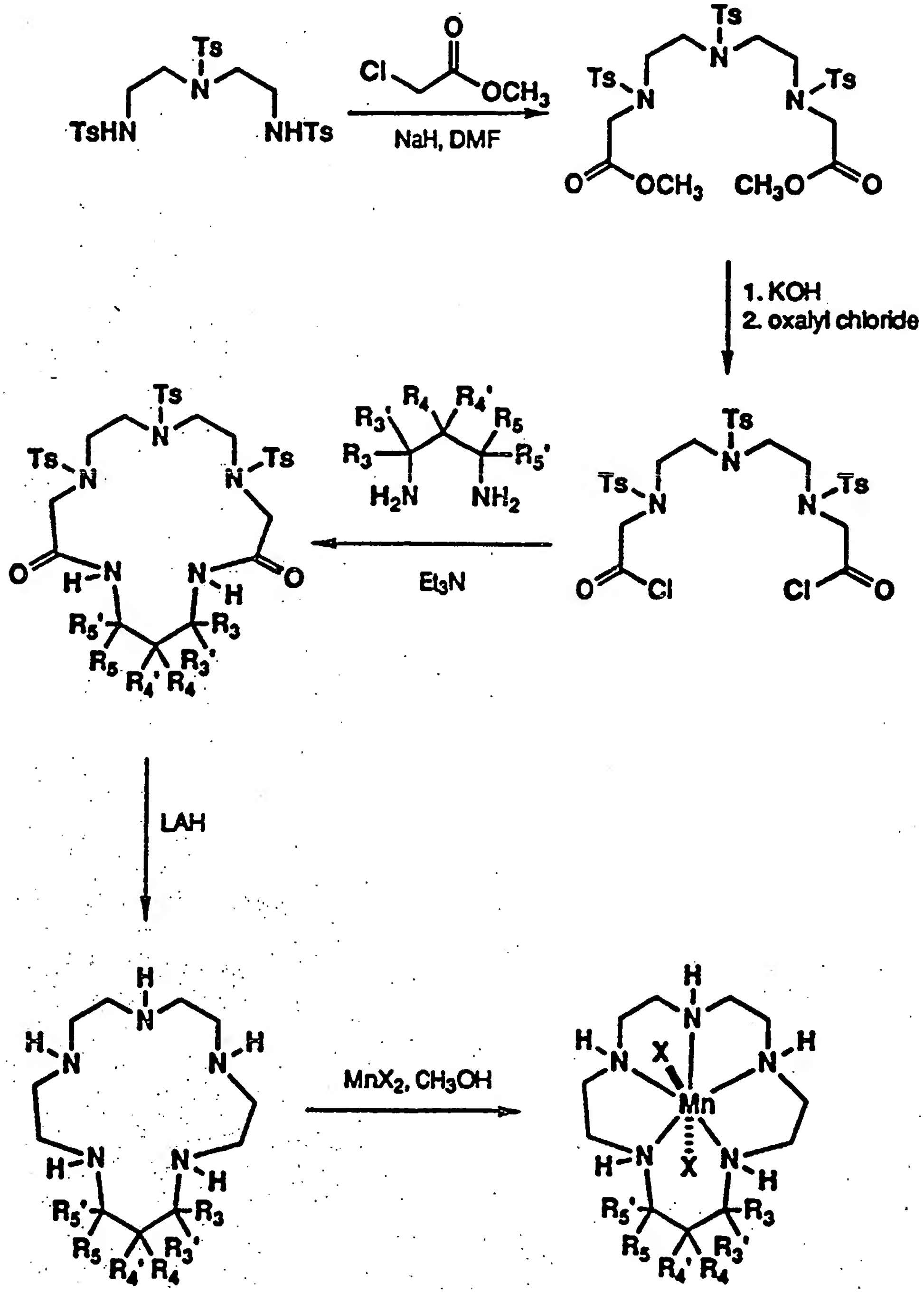


**Scheme M (Cont'd)**

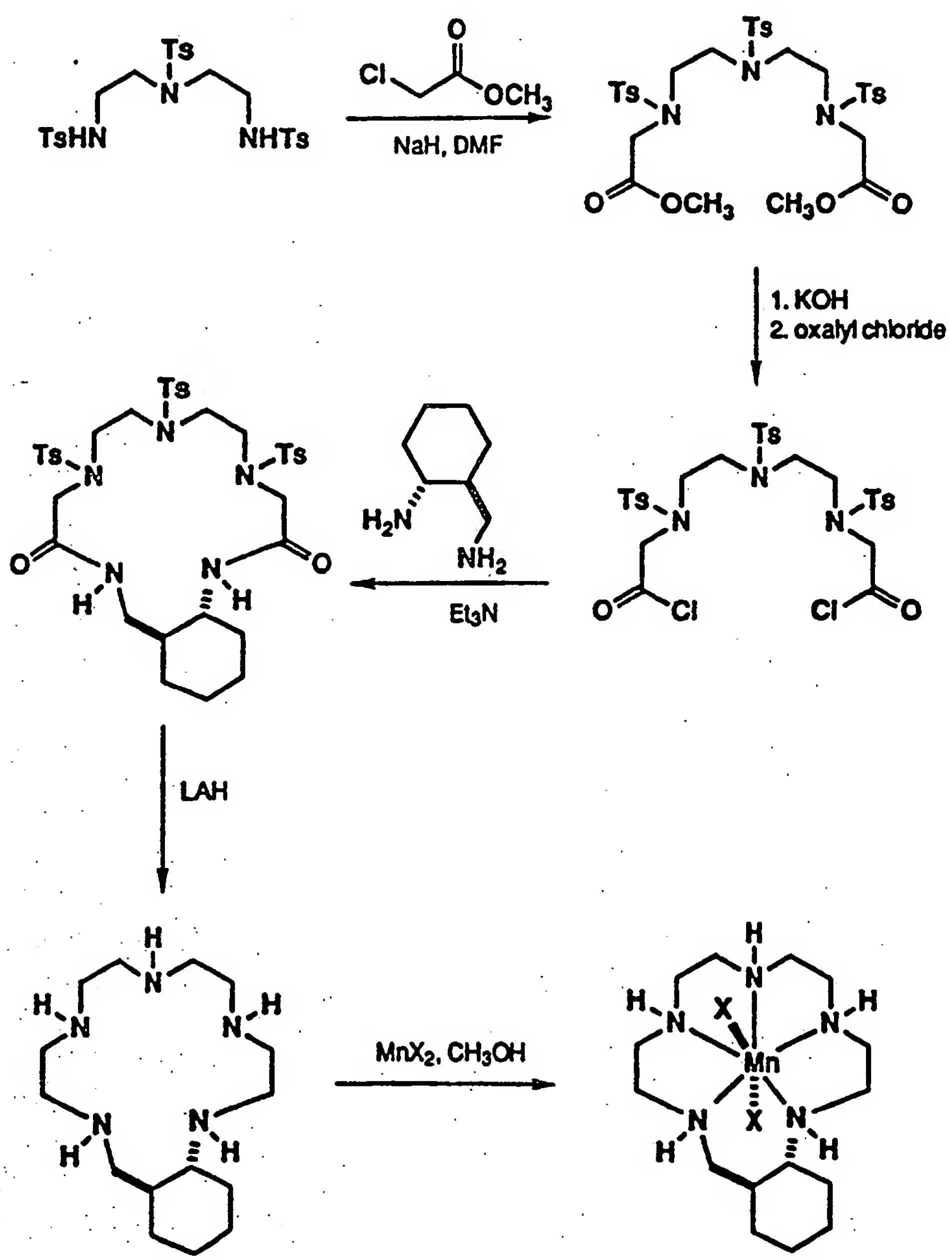


Scheme N

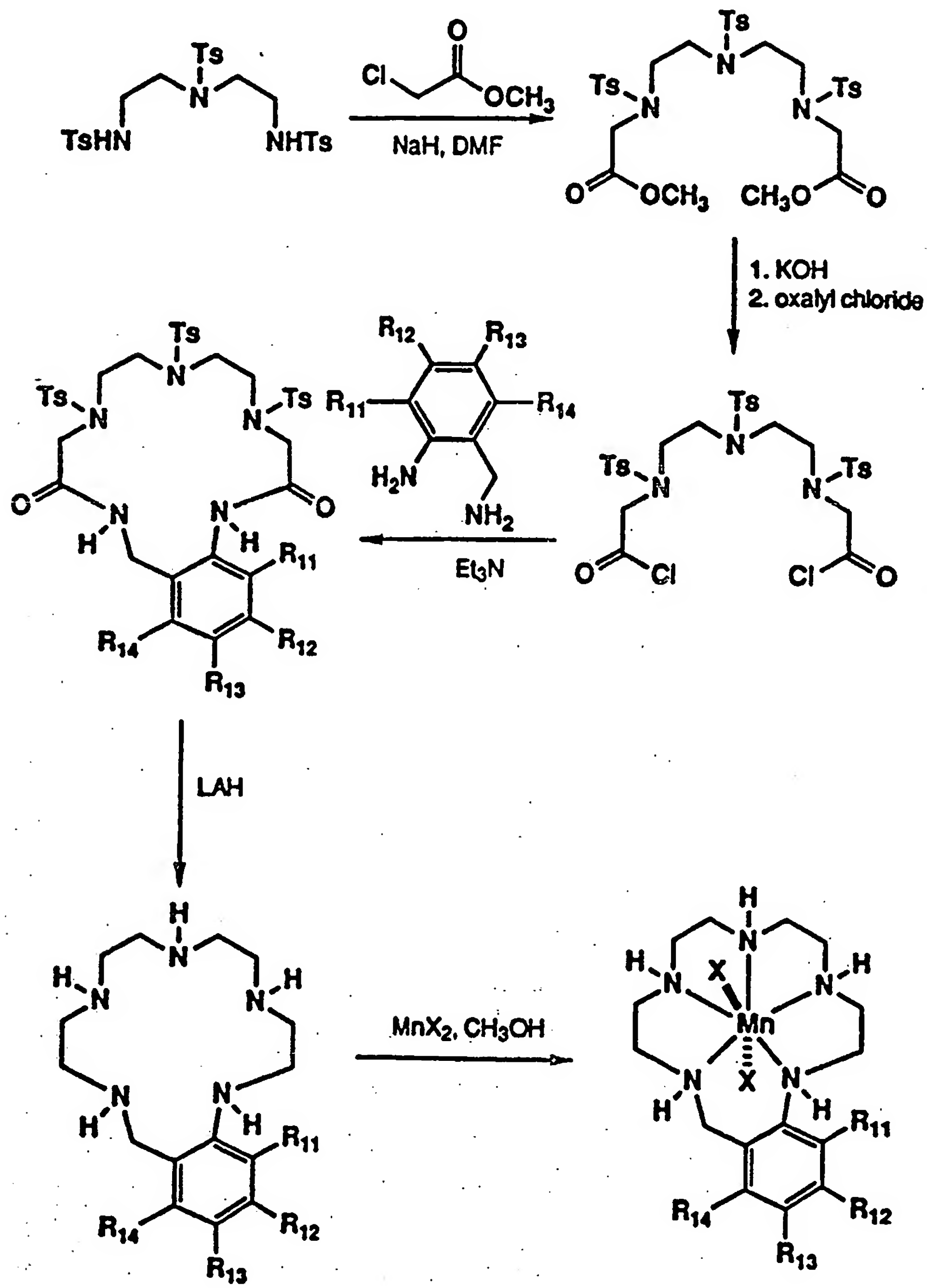
(General 1,3-diaminopropanes with tri-N-tosyl-diacid chloride)



Scheme O
(Aminomethylcyclohexylamines with tri-N-tosyl-diacid chloride)



**Scheme P**
**(Aminomethylanilines with tri-N-tosyl-diacid chloride)**



The pentaazamacrocycles of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for

| | |
|---|---|
| TsCl | Tosyl Chloride |
| DCC | Dicyclohexyl carbodiimide |
| LAH | Lithium aluminum hydride |

Example 1

A. Synthesis of 1.4.8.11-Tetra(p-toluenesulfonyl)-1,4,8,11-tetraazaundecane

To a stirred solution of p-toluenesulfonyl chloride (262 g, 1.37 mole) in anhydrous pyridine (600 ml) at 5°C was added a solution of 1,4,8,11-tetraazaundecane (49.1 g, 0.306 mole) in anhydrous pyridine (200 ml) under a dry argon atmosphere, maintaining the temperature <20°C. The addition required 1 h. The mixture was stirred overnight at room temperature. $H_2O$ (1.5 l) was slowly added to the cooled (ice bath) mixture. The resulting oil was dissolved in $CH_2Cl_2$, separated from the aqueous layer. The $CH_2Cl_2$ layer was washed with 5% HCl and $H_2O$ and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil which solidified on standing. The resulting solid was ground to a powder and dried in vacuo to give 186 g (78% yield) of the crude product: $^1$H NMR ($CDCl_3$) 6 1.98 (quint, J=7.3 Hz, 2 H), 2.40 (s, 6 H), 2.42 (s, 6 H), 3.11 (t, J=7.3 Hz, 4 H), 3.17 (s, 8 H), 5,76 (t, J=6.0 Hz, 2 H), 7.29 (m, 8 H), 7.64 (d, J=8.3 Hz, 4 H), 7.75 (d, J=8.3 Hz, 4 H).

B. Synthesis of 1.4.8.11-Tetra(p-toluenesulfonyl)-1,4,8,11-tetraazaundecane-1, 11-disodium Salt

To a stirred slurry of 1,4,8,11-tetra(p-toluenesulfonyl)-1,4,8,11-tetraazaundecane prepared as in Example 11A (80.0 g, 0.103 mole) in ethanol (140 ml) heated to reflux under a dry argon atmosphere was rapidly added a solution of sodium ethoxide (prepared by dissolving sodium metal (5.20 g, 0.227 mole) in ethanol (150 ml)). The brown solution was filtered while hot and the solvent was removed in vacuo to give the crude product as an oily solid: $^1$H NMR ($CDCl_3$) 1.71 (br s, 2 H), 2.26 (s, 6 H), 2.34 (s, 6 H), 2.79 (br m, 4 H), 2.99 (br m, 8 H), 6.90 (d, J=8.1 Hz, 4 H), 7.13 (d, J=8.3 Hz, 4 H), 7.50 (d, J=8.3 Hz, 4 H), 7.57 (d, J=8.1 Hz, 4 H).

C. Synthesis of 3-(p-Toluenesulfonyl)-3-azapentane-1,5-di-p-toluenesulfonate

To a stirred solution of p-toluenesulfonyl chloride (598 g, 3.14 mole) and triethylamine (318 g, 3.14 mole) in anhydrous $CH_2Cl_2$ (1.5 l) at 5°C under a dry argon atmosphere was added a solution of diethanolamine (100 g, 0.951 mole) in anhydrous $CH_2Cl_2$ (50 ml) maintaining the temperature <10°C. The addition required 45 minutes. The mixture was allowed to warm to room temperature and was stirred an additional 18 h. $H_2O$ (1.5 1) was then added and the $CH_2Cl_2$ layer was separated. The $CH_2Cl_2$ layer was washed with 10% HCl and $H_2O$ and was dried ($MgSO_4$). The solvent was removed in vacuo to give an off-white solid. The crude product was purified by recrystallization from ethyl acetate-hexane to give 329 g (61% yield) of the product as a white powder: mp 86-7.5°C; $^1$H NMR ($CDCl_3$) δ 2.42 (s,3 H), 2.46 (s, 6 H), 3.37 (t, J=6.0 Hz, 4 H), 4.11 (t, J=6.0 Hz, 4 H), 7.29 (d, J=7.7 Hz, 2 H), 7.36 (d, J=8.0 Hz, 4 H), 7.62 (d, J=8.4 Hz, 2 H), 7.77 (d, J=8.3 Hz,4 H).

D. Synthesis of 1,4,7,10,13-Penta(D-toluenesulfonyl)-1,4,7,10,13-pentaazacyclohexadecane

To a stirred solution of 1,4,8,11-tetra(p-toluenesulfonyl)-1,4,8,11-tetraazaundecane-1,11-disodium salt prepared as in Example 1B (74.0 g, 0.0901 mole) in anhydrous DMF (800 ml) was added sodium hydride (0.2 g-80% in mineral oil, 6.7 mmol). The unreacted sodium hydride was removed by filtration and the solution was heated to 100°C under a dry argon atmosphere. To this stirred solution was added a solution of 3-(p-toluenesulfonyl)-3-azapentane-1,5-di-p-toluenesulfonate prepared as in Example 1C (51.2 g, 0.0901 mole) in anhydrous DMF (400 ml) over a 3 h period, maintaining the temperature at 100°C. After stirring the solution an additional 1.25 h at 100°C, the mixture was concentrated in vacuo to a volume of 750 ml. $H_2O$ (2.3 1) was slowly added to crystallize the product. The resulting gummy solid was triturated with ethyl acetate and dried in vacuo to give 31 g (34% yield) of the crude product as a powder: mp 225-30°C, $^1$H NMR ($CDCl_3$) δ 1.90 (quint, J=6.0 Hz, 2 H), 2.42 (s, 9 H), 2.44 (s, 6 H), 3.07 (t, J=7.0 Hz, 4 H), 3.15 (m, 4 H), 3.28 (m, 12 H), 7.31 (m, 10 H), 7.67 (m, 10 H).

E. Synthesis of 1,4,7,10,13-Pentaazacyclohexadecane

A mixture of 1,4,7,10,13-penta(p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclohexadecane prepared as in Example ID (30 g, 0.030 mole) and concentrated $H_2SO_4$ (100 ml) was heated at 100°C with stirring under a dry argon atmosphere for 69 h. To the resulting brown solution, ethanol (200 mL) was added dropwise with stirring at 5°C, followed by ethyl ether (500 ml). The tan solid was filtered and washed thoroughly with ethyl ether. The solid was then dissolved in $H_2O$

(75 ml), the pH was adjusted to 10 with 10N NaOH, and the solution was extracted with $CHCl_3$ (6 x 200 ml). The extracts were combined and dried ($Na_2SO_4$), and the solvent was removed in vacuo. The resulting yellow solid was purified by recrystallization from hexane to give 1.0 g (15% yield) of the product as colorless needles: mp 109-110.5°C; $^1H$ NMR ($CDCl_3$) δ 1.72 (quint, J=5.4 Hz, 2 H), 1.76 (br s, 5 H), 2.73 (m, 20 H); Anal. calcd. for $C_{11}H_{27}N_5$: C, 57.60; H, 11.86; N, 30.53. Found: C, 57.77; H, 12.35; N, 30.57.

F. Synthesis of Manaanese(II)dichloro(1.4.7.10.13-pentaazacyclohexadecane)]

A solution of 1,4,7,10,13-pentaazacyclohexadecane prepared as in Example 1E (700 mg, 3.1 mmole) and anhydrous manganese(II) chloride (0.38 g, 3.1 mmole) in anhydrous MeOH (50 ml) was refluxed for 2 h under a dry nitrogen atmosphere. After cooling the solvent was removed in vacuo to give a solid. The solid was recrystallized from ethanol-ethyl ether to give 0.81 g (75% yield) of a white crystalline solid: FAB mass spectrum (NBA) m/z (relative intensity) 319/321 [(CM-Cl),+100/29]; $C_{11}H_{27}Cl_2MnN_5$; C, 37.19; H, 7.66; N, 19.72; Cl, 19.96. Found: C, 37.06; H, 7.64; N, 19.94; N, 19.94; Cl, 19.43.

Example 2

Stopped-Flow Kinetic Analysis

Stopped-flow kinetic analysis has been utilized to determine whether a compound can catalyze the dismutation of superoxide (Bull, C., McClune, G.J., and Fee, J.A., (1983) J. *Am. Chem. Soc.*, 105, 5290-5300. For the attainment of consistent and accurate measurements all reagents were biologically clean and metal-free. To achieve this, all buffers (Calbiochem) were biological grade, metal-free buffers and were handled with utensils which had been washed first with 0.1 N HCl, followed by purified water, followed by a rinse in a $10^{-4}$ M EDTA bath at pH 8, followed by a rinse with purified water and dried at 65°C for several hours. Dry DMSO solutions of potassium superoxide (Aldrich) were prepared under a dry, inert atmosphere of argon in a Vacuum Atmospheres dry glovebox using dried glassware. The DMSO solutions were prepared immediately before every stopped-flow experiment. A mortar and pestle were used to grind the yellow solid potassium superoxide (~100 mg). The powder was then ground with a few drops of DMSO and the slurry transferred to a flask containing an additional 25 ml of DMSO. The resultant slurry was stirred for 1/2 h and then filtered. This procedure gave reproducibly ~2 mM concentrations of superoxide in DMSO. These solutions were transferred to a glovebag under nitrogen in sealed vials prior to loading the syringe under nitrogen. It should be noted that the DMSO/superoxide solutions are extremely sensitive to water, heat, air, and extraneous metals. A fresh, pure solution has a very slight yellowish tint.

Water for buffer solutions was delivered from an in-house deionized water system to a Barnstead Nanopure Ultrapure Series 550 water system and then double distilled, first from alkaline potassium permanganate and then from a dilute EDTA solution. For example, a solution containing 1.0 g of potassium permanganate, 2 liters of water and additional sodium hydroxide necessary to bring the pH to 9.0 were added to a 2-liter flask fitted with a solvent distillation head. This distillation will oxidize any trace of organic compounds in the water. The final distillation was carried out under nitrogen in a 2.5-liter flask containing 1500 ml of water from the first still and 1.0 x $10^{-6}$M EDTA. This step will remove remaining trace metals from the ultrapure water. To prevent EDTA mist from volatilizing over the reflux arm to the still head, the 40-cm vertical arm was packed with glass beads and wrapped with insulation. This system produces deoxygenated water that can be measured to have a conductivity of less than 2.0 nanomhos/$cm^2$.

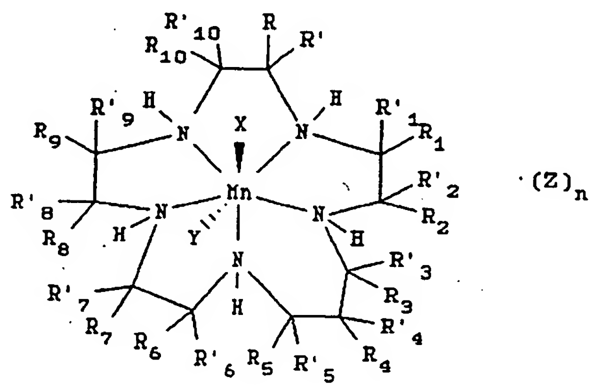
The stopped-flow spectrometer system was designed and manufactured by Kinetic Instruments Inc. (Ann Arbor, MI) and was interfaced to a MAC IICX personal computer. The software for the stopped-flow analysis was provided by Kinetics Instrument Inc. and was written in QuickBasic with MacAdios drivers. Typical injector volumes (0.10 ml of buffer and 0.006 ml of DMSO) were calibrated so that a large excess of water over the DMSO solution were mixed together. The actual ratio was approximately 17/1 so that the initial concentration of superoxide in the aqueous solution was in the range 60-120 µM. Since the published extinction coefficient of superoxide in $H_2O$ at 245 nm is ~2250 $M^{-1}$ $cm^{-1}$ (1), an initial absorbance value of approximately 0.3-0.5 would be expected for a 2-cm path length cell, and this was observed experimentally. Aqueous solutions to be mixed with the DMSO solution of superoxide were prepared using 80 mM concentrations of the Hepes buffer, pH 8.1 (free acid + Na form). One of the reservoir syringes was filled with 5 ml of the DMSO solution while the other was filled with 5 ml of the aqueous buffer solution. The entire injection block, mixer, and spectrometer cell were immersed in a thermostatted circulating water bath with a temperature of 21.0 ± 0.5°C.

Prior to initiating data collection for a superoxide decay, a baseline average was obtained by injecting several shots of the buffer and DMSO solutions into the mixing chamber. These shots were averaged and stored as the baseline. The first shots to be collected during a series of runs were with aqueous solutions that did not contain catalyst. This assures that each series of trials were free of contamination capable of generating first-order superoxide decay profiles.

If the decays observed for several shots of the buffer solution were second-order, solutions of manganese(II) complexes could be utilized. In general, the potential SOD catalyst was screened over a wide range of concentrations. Since the initial concentration of superoxide upon mixing the DMSO with the aqueous buffer was -1.2 x $10^{-4}$ M, we wanted to use a manganese (II) complex concentration that was at least 20 times less than the substrate superoxide. Consequently, we generally screened compounds for SOD activity using concentrations ranging from 5 x 10-7 to 8 x $10^{-6}$ M. Data acquired from the experiment was imported into a suitable math program (e.g., Cricket Graph) so that standard kinetic data analyses could be performed. The catalytic rate constant for dismutation of superoxide by the manganese (II) complex of Example 1 was determined from a linear plot of observed rate constant ($k_{obs}$) versus the concentration of the manganese(II) complex. The $k_{obs}$ value was obtained from a linear plot of ln absorbance at 245 nm versus time for the dismutation of superoxide by the manganese(II) complex. The $k_{cat}$ for the manganese(II) complex of Example 1 was found to be 1.1 x $10^6$ $M^{-1}sec^{-1}$ at pH = 8.1 and 21°C which indicates that the manganese(II) complex of Example 1 is an effective catalyst for the dismutation of superoxide.

## Claims

1. Pharmaceutical composition comprising a complex represented by the formula:



wherein R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ independently represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; $R_1$ or $R'_1$ and $R_2$ or $R'_2$, $R_3$ or $R'_3$ and $R_4$ or $R'_4$, $R_3$ or $R'_3$ and $R_5$ or $R'_5$, $R_4$ or $R'_4$ and $R_5$ or $R'_5$, $R_6$ or $R'_6$ and $R_7$ or $R'_7$, $R_8$ or $R'_8$, and $R_9$ or $R'_9$ and $R_{10}$ or $R'_{10}$ and R or R' together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R or R' and $R_1$ or $R'_1$, $R_2$ or $R'_2$ and $R_3$ or $R'_3$ or $R_4$ or $R'_4$, $R_4$ or $R'_4$ or $R_5$ or $R'_5$ and $R_6$ or $R'_6$, $R_7$ or $R'_7$ and $R_8$ or $R'_8$, and $R_9$ or $R'_9$ and $R_{10}$ or $R'_{10}$ together with the carbon atoms to which they are attached independently form a nitrogen containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', $R_1$ and $R'_1$, $R_2$ and $R'_2$, $R_3$ and $R'_3$, $R_4$ and $R'_4$, $R_5$ and $R'_5$, $R_6$ and $R'_6$, $R_7$ and $R'_7$, $R_8$ and $R'_8$, $R_9$ and $R'_9$, and $R_{10}$ and $R'_{10}$ together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; and one of R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ together with a different one of R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ and $R'_{10}$ which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium,

thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations thereof; wherein X, Y and Z are ligands independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid , aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea,alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof, or X, Y and Z are independently attached to one or more of the "R" groups and n is an integer from 0 to 3; wherein, alkyl, alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to 22 carbon atoms; alkenyl, alone or in combination, means an alkyl radical having one or more double bonds; alkynyl, alone or in combination, means an alkyl radical having one or more triple bonds; cycloalkyl, alone or in combination, means a cycloalkyl radical containing from 3 to 10 carbon atoms; cycloalkylalkyl means an alkyl radical substituted by a cycloalkyl radical, both as defined above; cycloalkylcycloalkyl means a cycloalkyl radical substituted by another cycloalkyl radical, both as defined above; cycloalkenyl, alone or in combination, means a cycloalkyl radical having one or more double bonds; cycloalkenylalkyl means an alkyl radical substituted by a cycloalkenyl radical, both as defined above; alkylcycloalkyl and alkenylcycloalkyl mean a cycloalkyl radical substituted by an alkyl or alkenyl radical, as defined above; alkylcycloalkenyl and alkenylcycloalkenyl mean a cycloalkenyl radical substituted by an alkyl or alkenyl radical, as defined above; aryl alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents; aralkyl, alone or in combination, means an alkyl or cycloalkyl radical in which one hydrogen atom is replaced by an aryl radical as defined above; heterocyclic means ring structures containing at least one other kind of atom in addition to carbon in the ring; saturated, partially saturated or unsaturated cyclic means fused ring structures in which 2 carbons of the ring are also part of the 16-membered macrocyclic ligand; saturated, partially saturated or unsaturated ring structure means a ring structure in which one carbon of the ring is also part of the 16-membered macrocyclic ligand; and nitrogen-containing heterocycle means ring structures in which 2 carbons and a nitrogen of the ring are also part of the 16-membered macrocyclic ligand; and wherein any of the R groups defined above can optionally carry one or more substituents; and a nontoxic, pharmaceutically acceptable carrier, adjuvant or vehicle.

2. Composition of Claim 1 wherein R is selected from the group consisting of hydrogen and alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoalkyl and o-hydroxybenzyl radicals and $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$, $R'_{10}$ and R' are hydrogen.

3. Composition of Claim 2 wherein R is selected from the group consisting of hydrogen and methyl, isobutyl, propargyl, cyclohexylmethyl, benzyl, phenyl,cyclohexyl, 4-benzyloxybenzyl, o-hydroxybenzyl, aminobutyl and octadecyl radicals.

4. Composition of Claim 1 wherein at least one of $R_1$ or $R'_1$ and $R_2$ or $R'_2$, $R_3$ or $R'_3$ and $R_4$ or $R'_4$, $R_3$ or $R'_3$ and $R_5$ or $R'_5$, $R_4$ or $R'_4$ and $R_5$ or $R'_5$, $R_6$ or $R'_6$ and $R_7$ or $R'_7$, $R_8$ or $R'_8$ and $R_9$ or $R'_9$, and $R_{10}$ or $R'_{10}$ and R or R' together with the carbon atoms to which they are attached form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms, or at least one of R or R' and $R_1$ or $R'_1$, $R_2$ or $R'_2$ and $R_3$ or $R'_3$ or $R_4$ or $R'_4$, or $R_4$ or $R'_4$ or $R_5$ or $R'_5$ and $R_6$ or $R'_6$, $R_7$ or $R'_7$ and $R_8$ or $R'_8$, and $R_9$ or $R'_9$ and $R_{10}$ or $R'_{10}$ together with the carbon atoms to which they are attached form a nitrogen containing heterocycle having 2 to 20 carbon atoms; and all of the remaining "R" groups are independently selected from hydrogen or alkyl groups.

5. Composition of Claim 4 wherein at least one of $R_1$ or $R'_1$ and $R_2$ or $R'_2$, $R_3$ or $R'_3$ and $R_4$ or $R'_4$, $R_3$ or $R'_3$ and $R_5$

or $R'_5$, $R_4$ or $R'_4$ and $R_5$ or $R'_5$, $R_6$ or $R'_6$ and $R_7$ or $R'_7$, $R_8$ or $R'_8$ and $R_9$ or $R'_9$, and $R_{10}$ or $R'_{10}$ and R or R' together with the carbon atoms to which they are attached is a cyclohexano group, and all of the remaining "R" groups are hydrogen or alkyl groups.

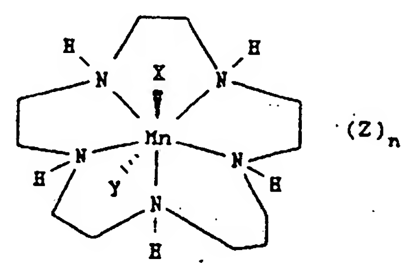
6. Composition of Claim 1 wherein X, Y and Z are independently selected from the group consisting of halide, organic acid, nitrate and bicarbonate anions.

7. Use of a complex according to Claim 1 for the manufacture of a medicament for preventing or treating a disease or disorder which is mediated, at least in part, by superoxide.

8. Use in accordance with Claim 7 wherein said disease or disorder is selected from ischemic reperfusion injury, myocardial infarction, metastasis, hypertension, surgically-induced ischemia, inflammatory bowel disease, rheumaoid arthritis, atherosclerosis, thrombosis, platelet aggregation, oxidant-induced tissue injuries and damage, ostearthritis, psoriasis, organ transplant rejections, impotence, radiation-induced injury, asthma, influenza, stroke, burns, trauma, acute pancreatitis, pyelonephritis, hepatitis, autoimmune diseases, insulinedependent diabetes mellitus, disseminated intravascular coagulation, fatty embolism, adult and infantile respiratory distress, carcinogenesis and hemorrhages in neonates.

9. Use in accordance with Claim 8 wherein said disease or disorder is selected from ischemic reperfusion injury, myocardial infraction, stroke and atherosclerosis.

10. Use in accordance with Claim 9 wherein said complex is represented by the formula

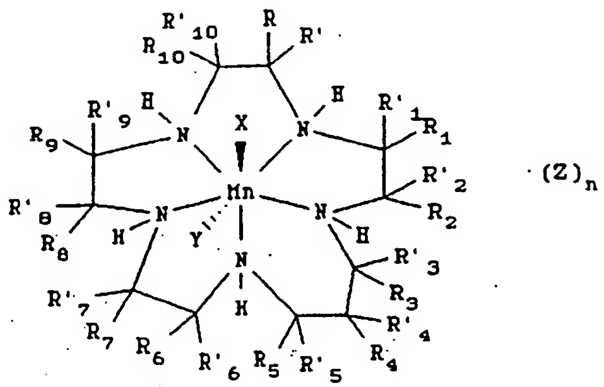


11. Use in accordance with Claim 10 wherein n is 0 and X and Y are Cl.

12. Use of a composition according to Claim 1 for the manufacture of a medicament for preventing or treating a disease or disorder which is mediated at least in part by superoxide or oxygen radicals derived therefrom.

## Patentansprüche

1. Pharmazeutische Zusammensetzung, umfassend einen Komplex der Formel:



worin R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ und $R'_{10}$ unbhängig Wasserstoff, Alkyl, Alkenyl, Alkinyl, Cycloalkyl, Cycloalkenyl, Cycloalkylalkyl, Cycloalkylcycloalkyl, Cycloalkenylalkyl, Alkylcyclo-alkyl, Alkylcycloalkenyl, Alkenylcycloalkyl, Alkenylcycloalkenyl, heterocyclische, Aryl- und Aralkylreste bedeuten; $R_1$ oder $R'_1$ und $R_2$ oder $R'_2$, $R_3$ oder $R'_3$ und $R_4$ oder $R'_4$, $R_3$ oder $R'_3$ und $R_5$ oder $R'_5$, $R_4$ oder $R'_4$ und $R_5$ oder $R'_5$, $R_6$ oder $R'_6$ und $R_7$ oder $R'_7$, $R_8$ oder $R'_8$, und $R_9$ oder $R'_9$ und $R_{10}$ oder $R'_{10}$ und R oder R' zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, unabhängig einen gesättigten, teilweise gesättigten oder ungesättigten Cyclus mit 3 bis 20 Kohlenstoffatomen bilden; R oder R' und $R_1$ oder $R'_1$, $R_2$ oder $R'_2$ und $R_3$ oder $R'_3$ oder $R_4$ oder $R'_4$, $R_4$ oder $R'_4$ oder $R_5$ oder $R'_5$ und $R_6$ oder $R'_6$, $R_7$ oder $R'_7$ und $R_8$ oder $R'_8$, und $R_9$ oder $R'_9$ und $R_{10}$ oder $R'_{10}$ zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, unabhängig einen Stickstoff enthaltenden Heterocyclus mit 2 bis 20 Kohlenstoffatomen bilden, mit der Maßgabe, daß, wenn der Stickstoff enthaltende Heterocyclus ein aromatischer Heterocyclus ist, der keinen an den Stickstoff gebundenen Wasserstoff enthält, der an den Stickstoff gebundene Wasserstoff, wie in der obigen Formel gezeigt, welcher Stickstoff auch im makrocyclischen Liganden oder Komplex vorliegt, und die an dieselben Kohlenstoffatome des Makrocyclus gebundenen Gruppen R fehlen; R und R', $R_1$ und $R'_1$, $R_2$ und $R'_2$, $R_3$ und $R'_3$, $R_4$ und $R'_4$, $R_5$ und $R'_5$, $R_6$ und $R'_6$, $R_7$ und $R'_7$, $R_8$ und $R'_8$, $R_9$ und $R'_9$, $R_{10}$ und $R'_{10}$ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, unabhängig eine gesättigte, teilweise gesättigte oder ungesättigte Ringstruktur mit 3 bis 20 Kohlenstoffatomen bilden; und eines von R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ und $R'_{10}$ zusammen mit einem anderen von R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ und $R'_{10}$, das an ein anderes Kohlenstoffatom im makrocyclischen Liganden gebunden ist, gebunden sein kann, um eine Folge der Formel zu bilden:

$$-\!\!(CH_2)_x\!-M-\!(CH_2)_w\!-L-\!(CH_2)_z\!-J-\!(CH_2)_y\!-$$

worin w, x, y und z unabhängig ganze Zahlen von Null bis 10 sind, und M, L und J unabhängig ausgewählt sind aus der Gruppe bestehend aus Alkyl, Alkenyl, Alkinyl, Aryl, Cycloalkyl, Heteroaryl, Alkaryl, Alkheteroaryl, Aza, Amid, Ammonium, Thia, Sulfonyl, Sulfinyl, Sulfonamid, Phosphonyl, Phosphinyl, Phosphino, Phosphonium, Keto, Ester, Carbamat, Harnstoff, Thio-carbonyl, Boraten, Boranen, Boraza, Silyl, Siloxy, Silaza und Kombinationen hievon; und Kombinationen hievon; worin X, Y und Z Liganden darstellen, unabhängig ausgewählt aus der Gruppe bestehend aus Halogenid, Oxo, Aquo, Hydroxo, Alkohol, Phenol, Di-oxygen, Peroxo, Hydroperoxo, Alkylperoxo, Arylperoxo, Ammoniak, Alkylamino, Arylamino, Heterocycloalkylamino, Heterocycloarylamino, Aminoxiden, Hydrazin, Alkylhydrazin, Arylhydrazin, Stickstoffoxid, Cyanid, Cyanat, Thiocyanat, Isocyanat, Isothiocyanat, Alkylnitril, Arylnitril, Alkylisonitril, Arylisonitril, Nitrat, Nitrit, Azido, Alkylsulfonsäure, Arylsulfonsäure, Alkylsulfoxid, Arylsulfoxid, Alkylarylsulfoxid, Alkylsulfensäure, Arylsulfensäure, Alkylsulfinsäure, Arylsulfinsäure, Alkylthiolcarbonsäure, Arylthiolcarbonsäure, Alkylthiolthiocarbonsäure, Arylthiolthiocarbonsäure, Alkylcarbonsäure, Arylcarbonsäure, Harnstoff, Alkylharnstoff, Arylharnstoff, Alkylarylharnstoff, Thioharnstoff, Alkylthioharnstoff, Arylthioharnstoff, Alkylarylthioharnstoff, Sulfat, Sulfit, Bisulfat, Bisulfit, Thiosulfat, Thiosulfit, Hydrosulfit, Alkylphosphin, Arylphosphin, Alkylphosphinoxid, Arylphosphinoxid, Alkylarylphosphinoxid, Alkylphosphinsulfid, Arylphosphinsulfid, Alkylarylphosphinsulfid, Alkylphosphonsäure, Arylphosphonsäure, Alkylphosphinsäure, Arylphosphinsäure, Alkylphosphinige Säure, Arylphosphinige Säure, Phosphat, Thiophosphat, Phosphit, Pyrophosphit, Triphosphat, Hydrogenphosphat, Dihydrogenphosphat, Alkylguanidino, Arylguanidino, Alkylarylguanidino, Alkylcarbamat, Arylcarbamat, Alkylarylcarbamat, Alkylthiocarbamat, Arylthiocarbamat, Alkylarylthiocarbamat, Alkyldithiocarbamat,

Aryldithiocarbamat, Alkylaryldithiocarbamat, Bicarbonat, Carbonat, Perchlorat, Chlorat, Chlorit, Hypochlorit, Perbromat, Bromat, Bromit, Hypobromit, Tetrahalogenmanganat, Tetrafluorborat, Hexafluorantimonat, Hypophosphit, Iodat, Periodat, Metaborat, Tetraarylborat, Tetraalkylborat, Tartrat, Salicylat, Succinat, Citrat, Ascorbat, Saccharinat, Aminosäure, Hydroxamsäure, Thiotosylat, und Anionen von Ionenaustauscherharzen, oder den entsprechenden Anionen hievon, oder X, Y und Z unabhängig an eine oder mehrere der Gruppen "R" gebunden sind, und n eine ganze Zahl von 0 bis 3 ist; wobei Alkyl, allein oder in Kombination, einen geradkettigen oder verzweigtkettigen Alkylrest mit 1 bis 22 Kohlenstoffatomen bedeutet; Alkenyl, allein oder in Kombination, einen Alkylrest mit einer oder mehreren Doppelbindungen darstellt; Alkinyl, allein oder in Kombination, ein Alkylrest mit einer oder mehreren Dreifachbindungen ist; Cycloalkyl, allein oder in Kombination, einen Cycloalkylrest mit 3 bis 10 Kohlenstoffatomen bedeutet; Cycloalkylalkyl, allein oder in Kombination, einen Alkylrest, substituiert durch einen Cycloalkylrest, beide wie oben definiert, darstellt; Cycloalkylcycloalkyl ein Cycloalkylrest, substituiert durch einen weiteren Cycloalkylrest, beide wie oben definiert, ist; Cycloalkenyl, allein oder in Kombination, einen Cycloalkylrest mit einer oder mehreren Doppelbindungen bedeutet; Cycloalkenylalkyl einen Alkylrest, substituiert durch einen Cycloalkenylrest, beide wie oben definiert, darstellt; Alkylcycloalkyl und Alkenylcycloalkyl ein Cycloalkylrest, substituiert durch einen Alkyl- oder Alkenylrest, wie oben definiert, sind; Alkylcycloalkenyl und Alkenylcycloalkenyl einen Cycloalkenylrest, substituiert durch einen Alkyl- oder Alkenylrest, wie oben definiert, bedeuten; Aryl, allein oder in Kombination, einen Phenyl- oder Naphthylrest darstellt, der gegebenenfalls einen oder mehrere Substituenten trägt; Aralkyl, allein oder in Kombination, ein Alkyl- oder Cycloalkylrest ist, worin ein Wasserstoffatom durch einen Arylrest, wie oben definiert, ersetzt ist; heterocyclisch Ringstrukturen bedeutet, die zumindest eine andere Atomart zusätzlich zum Kohlenstoff im Ring enthalten; gesättigter, teilweise gesättigter oder ungesättigter Cyclus kondensierte Ringstrukturen bedeutet, worin 2 Kohlenstoffe des Rings auch ein Teil des 16-gliedrigen makrocyclischen Liganden sind; gesättigte, teilweise gesättigte oder ungesättigte Ringstruktur eine Ringstruktur bedeutet, worin ein Kohlenstoff des Rings auch ein Teil des 16-gliedrigen makrocyclischen Liganden ist; und Stickstoff enthaltender Heterocyclus Ringstrukturen bedeutet, worin 2 Kohlenstoffe und ein Stickstoff des Rings auch ein Teil des 16-gliedrigen makrocyclischen Liganden sind; und wobei irgendeine der oben definierten Gruppen R gegebenenfalls einen oder mehrere Substituenten tragen kann; und einen nicht-toxischen, pharmazeutisch annehmbaren Träger, ein Adjuvans oder ein Vehikel.

2. Zusammensetzung nach Anspruch 1, worin R ausgewählt ist aus der Gruppe bestehend aus Wasserstoff und Alkyl-, Cycloalkyl-, Cycloalkylalkyl-, Aryl-, Aralkyl-, Aminoalkyl- und o-Hydroxybenzylresten, und $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$, $R'_{10}$ und R' Wasserstoff bedeuten.

3. Zusammensetzung nach Anspruch 2, worin R ausgewählt ist aus der Gruppe bestehend aus Wasserstoff und Methyl-, Isobutyl-, Propargyl-, Cyclohexylmethyl-, Benzyl-, Phenyl-, Cyclohexyl-, 4-Benzyloxybenzyl-, o-Hydroxybenzyl-, Aminobutyl- und Octadecylresten.

4. Zusammensetzung nach Anspruch 1, worin zumindest eines von $R_1$ oder $R'_1$ und $R_2$ oder $R'_2$, $R_3$ oder $R'_3$ und $R_4$ oder $R'_4$, $R_3$ oder $R'_3$ und $R_5$ oder $R'_5$, $R_4$ oder $R'_4$ und $R_5$ oder $R'_5$, $R_6$ oder $R'_6$ und $R_7$ oder $R'_7$, $R_8$ oder $R'_8$ und $R_9$ oder $R'_9$, und $R_{10}$ oder $R'_{10}$ und R oder R' zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen gesättigten, teilweise gesättigten oder ungesättigten Cyclus mit 3 bis 20 Kohlenstoffatomen bildet, oder zumindest eines von R oder R' und $R_1$ oder $R'_1$, $R_2$ oder $R'_2$ und $R_3$ oder $R'_3$ oder $R_4$ oder $R'_4$, oder $R_4$ oder $R'_4$ oder $R_5$ oder $R'_5$ und $R_6$ oder $R'_6$, $R_7$ oder $R'_7$ und $R_8$ oder $R'_8$, und $R_9$ oder $R'_9$ und $R_{10}$ oder $R'_{10}$ zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Stickstoff enthaltenen Heterocyclus mit 2 bis 20 Kohlenstoffatomen bildet; und alle der übrigen Gruppen "R" unabhängig ausgewählt sind aus Wasserstoff oder Alkyl-Gruppen.

5. Zusammensetzung nach Anspruch 4, worin zumindest eines von $R_1$ oder $R'_1$ und $R_2$ oder $R'_2$, $R_3$ oder $R'_3$ und $R_4$ oder $R'_4$, $R_3$ oder $R'_3$ und $R_5$ oder $R'_5$, $R_4$ oder $R'_4$und $R_5$ oder $R'_5$, $R_6$ oder $R'_6$ und $R_7$ oder $R'_7$, $R_8$ oder $R'_8$ und $R_9$ oder $R'_9$, und $R_{10}$ oder $R'_{10}$ und R oder R' zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, eine Cyclohexano-Gruppe darstellt; und alle der übrigen Gruppen "R" Wasserstoff oder Alkyl-Gruppen bedeuten.

6. Zusammensetzung nach Anspruch 1, worin X, Y und Z unabhängig ausgewählt sind aus der Gruppe bestehend aus Halogenid, organischer Säure, Nitrat- und Bicarbonat-Anionen.

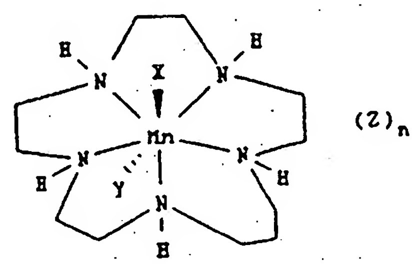
7. Verwendung eines Komplexes nach Anspruch 1 bei der Herstellung eines Medikaments zur Prävention oder Behandlung einer Erkrankung oder Störung, die, zumindest teilweise, durch Superoxid vermittelt wird.

8. Verwendung nach Anspruch 7, wobei die Erkrankung oder Störung ausgewählt ist aus ischämischer Reperfusi-

onsverletzung, Myokardinfarkt, Metastasen, Hypertension, chirurgisch induzierter Ischämie, entzündlichen Darmerkrankungen, rheumatoider Arthritis, Atherosklerose, Thrombose, Plättchenaggregation, Oxidans-induzierten Gewebeverletzungen und -schädigungen, Osteoarthritis, Psoriasis, Organtransplantatabstoßungen, Impotenz, durch Strahlung induzierten Verletzungen, Asthma, Influenza, Schlaganfall, Verbrennungen, Trauma, akuter Pankreatitis, Pyelonephritis, Hepatitis, Autoimmunkrankheiten, Insulin-abhängigem Diabetes mellitus, disseminierter intravaskulärer Koagulation, Fettembolie, Atemnot bei Erwachsenen und Neugeborenen, Karzinogenese und Blutungen bei Neugeborenen.

9. Verwendung nach Anspruch 8, wobei die Erkrankung oder Störung ausgewählt ist aus ischämischer Reperfusionsverletzung, Myokardinfarkt, Schlaganfall und Atherosklerose.

10. Verwendung nach Anspruch 9, wobei der Komplex die Formel aufweist:

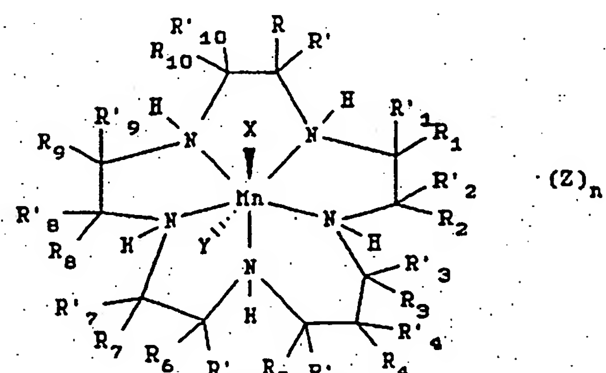



11. Verwendung nach Anspruch 10, wobei n Null ist, und X und Y die Bedeutung Cl haben.

12. Verwendung einer Zusammensetzung nach Anspruch 1 bei der Herstellung eines Medikaments zur Prävention oder Behandlung einer Erkrankung oder Störung, die zumindest teilweise durch Superoxid oder hievon stammende Sauerstoff-Radikale vermittelt wird.

**Revendications**

1. Composition pharmaceutique comprenant un complexe représenté par la formule :




dans laquelle les groupes R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ et $R'_{10}$, représentent, indépendamment, un atome d'hydrogène, un groupe alkyle, alcényle, alcynyle, cycloalkyle, cycloalcényle, cycloalkylalkyle, cycloalkylcycloalkyle, cycloalcénylalkyle, alkylcycloalkyle, alkylcycloalcényle, alcénylcycloalkyle, alcénylcycloalcényle, hétérocyclique, aryle et aralkyle ;
$R_1$ ou $R'_1$ et $R_2$ ou $R'_2$, $R_3$ ou $R'_3$ ou $R_4$ ou $R'_4$, $R_3$ ou $R'_3$ et $R_5$ ou $R'_5$, $R_4$ ou $R'_4$ et $R_5$ ou $R'_5$, $R_6$ ou $R'_6$ et $R_7$ ou

$R'_7$, $R_8$ ou $R'_8$ et $R_9$ ou $R'_9$ et $R_{10}$ ou $R'_{10}$ et R ou R' pris ensemble avec les atomes de carbone auxquels ils sont attachés forment, indépendamment, un groupe cyclique saturé, partiellement saturé ou insaturé comprenant de 3 à 20 atomes de carbone ; R ou R' et $R_1$ ou $R'_1$, $R_2$ ou $R'_2$ et $R_3$ ou $R'_3$ ou $R_4$ ou $R'_4$, $R_4$ ou $R'_4$ ou $R_5$ ou $R'_5$ et $R_6$ ou $R'_6$, $R_7$ ou $R'_7$ et $R_8$ ou $R'_8$, et $R_9$ ou $R'_9$ et $R_{10}$ ou $R'_{10}$ pris ensemble avec des atomes de carbone auxquels ils sont attachés forment, indépendamment, un hétérocycle contenant de l'azote, comprenant de 2 à 20 atomes de carbone, sous réserve que lorsque l'hétérocycle contenant de l'azote est un hétérocycle aromatique qui ne contient pas d'hydrogène attaché à l'azote, l'hydrogène attaché à l'azote, comme indiqué dans la formule ci-dessus, lequel atome d'azote se trouve également dans le ligand ou complexe macrocyclique, et les groupes R attachés aux mêmes atomes de carbone du macrocycle sont absents ; R et R', $R_1$ et $R'_1$, $R_2$ et $R'_2$, $R_3$ et $R'_3$, $R_4$ et $R'_4$, $R_5$ et $R'_5$, $R_6$ et $R'_6$, $R_7$ et $R'_7$, $R_8$ et $R'_8$, $R_9$ et $R'_9$, et $R_{10}$ et $R'_{10}$, pris ensemble avec l'atome de carbone auquel ils sont attachés, forment indépendamment, une structure cyclique saturée, partiellement saturée ou insaturée, comprenant de 3 à 20 atomes de carbone ; et l'un de R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ et $R'_{10}$ pris ensemble avec l'un de R, R', $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$ et $R'_{10}$ différent et qui est attaché à un atome de carbone différent du ligand macrocyclique, peuvent être liés pour former une bande représentée par la formule

$$-(CH_2)_x\ M-(CH_2)_w\ L-(CH_2)_z\ J-(CH_2)_y$$

dans laquelle w, x, y et z représentent, indépendamment, des nombres entiers allant de 0 à 10 et M, L et J sont choisis, indépendamment, dans le groupe formé par les radicaux alkyle, alcényle, alcynyle, aryle, cycloalkyle, hétéroaryle, alcaryle, alkhétéroaryle, aza, amide, ammonium, thia, sulfonyle, sulfinyle, sulfonamide, phosphonyle, phosphinyle, phosphino, phosphonium, céto, ester, carbamate, urée, thiocarbonyle, borates, boranes, boraza, silyle, siloxy, silaza et leurs combinaisons ; X, Y et Z représentent des ligands choisis indépendamment dans le groupe formé par les constituants ci-après : halogénure, oxo, aquo, hydroxo, alcool, phénol, dioxygène, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonium, alkylamino, arylamino, hétérocycloalkyle amino, hétérocycloaryle amino, oxydes d'amine, hydrazine, alkyle hydrazine, aryle hydrazine, oxyde nitrique, cyanure, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrure, azido, acide alkylsulfonique, acide arylsulfonique, alkyl sulfoxyde, aryl sulfoxyde, alkyl aryl sulfoxyde, acide alkyl sulfénique, acide aryl sulfénique, acide alkyl sulfinique, acide aryl sulfinique, acide alkyl thiol carboxylique, acide aryl thiol carboxylique, acide alkyl thiol thiocarboxylique, acide aryl thiol thiocarboxylique, acide alkyl carboxylique, acide aryl carboxylique, urée, alkyl urée, aryl urée, alkyl aryl urée, thio-urée, alkylthio-urée, arylthio-urée, alkylarylthio-urée, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, oxyde d'alkylphosphine, oxyde d'arylphosphine, oxyde d'alkylaryl phosphine, sulfure d'alkyl phosphine sulfure d'aryl phosphine, sulfure d'alkyl aryl phosphine, acide alkyl phosphonique, acide aryl phosphonique, acide alkyl phosphinique, acide aryl phosphinique, acide alkyl phosphineux, acide aryl phosphineux, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, phosphate acide, phosphate diacide, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, carbamate d'alkyle, carbamate d'aryle, carbamate d'alkylaryle, thiocarbamate d'alkyle, thiocarbamate d'aryle, thiocarbamate d'alkylaryle, dithiocarbamate d'alkyle, dithiocarbamate d'aryle, dithiocarbamate d'alkylaryle, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tétrahalogénomanganate, tétrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, métaborate, tétra-arylborate, tétra-alkylborate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino-acide, acide hydroxamique, thiotosylate, et anions de résine échangeuse d'ions, ou les anions correspondant à ces derniers, ou bien X, Y et Z sont indépendamment attachés, à un ou plusieurs groupes "R" et n représente un nombre entier de 0 à 3 ; dans ce qui précède, alkyle, seul ou en combinaison, signifie un radical alkyle à chaîne droite ou ramifiée contenant de 1 à 22 atomes de carbone ; alcényle, seul ou en combinaison, signifie un radical alkyle comprenant une ou plusieurs doubles liaisons ; alcynyle, seul ou en combinaison, signifie un radical alkyle comprenant une ou plusieurs triples liaisons ; cycloalkyle, seul ou en combinaison, signifie un radical cycloalkyle contenant de 3 à 10 atomes de carbone ; cycloalkylalkyle signifie un radical alkyle substitué par un radical cycloalkyle, les deux comme défini ci-dessus ; cycloalkylcycloalkyle signifie un radical cycloalkyle substitué par un autre radical cycloalkyle, les deux comme défini ci-dessus ; cycloalcényle, seul ou en combinaison, signifie un radical cycloalkyle comprenant une ou plusieurs doubles liaisons ; cycloalcénylalkyle signifie un radical alkyle substitué par un radical cycloalcényle, les deux comme défini ci-dessus ; alkylcycloalkyle et alcénylcycloalkyle signifie un radical cycloalkyle substitué par un radical alkyle ou alcényle, comme défini ci-dessus ; alkylcycloalcényle et alcénylcycloalcényle signifient un radical cycloalcényle substitué par un radical alkyle ou alcényle, comme défini ci-dessus ; aryle, seul ou en combinaison, signifie un radical phényle ou naphtyle qui porte facultativement un ou plusieurs substituants ; aralkyle, seul ou en combinaison, signifie un radical alkyle ou cycloalkyle dans lequel un atome d'hydrogène est remplacé par un radical aryle comme défini ci-dessus ; noyau hétérocyclique

signifie des structures cycliques contenant dans le cycle au moins un autre type d'atome en plus de l'atome de carbone ; cyclique saturé, partiellement saturé ou insaturé signifie des structures de cycles condensés dans lesquelles deux atomes de carbone du cycle font également partie du ligand macrocyclique hexadécagonal comprenant 16 membres ; structure cyclique saturée, partiellement saturée ou insaturée signifie une structure cyclique dans laquelle un atome de carbone du cycle fait également partie du ligand macrocyclique comprenant 16 membres ; et hétérocycle contenant de l'azote signifie des structures de cycle dans lesquelles 2 atomes de carbone et un atome d'azote du cycle font également partie du ligand macrocyclique comprenant 16 membres ; et où n'importe lequel des groupes R définis ci-dessus peut porter facultativement un ou plusieurs substituants ; et un véhicule, véhiculeur ou adjuvant non toxique, pharmaceutiquement acceptable.

2. Composition selon la revendication 1, dans laquelle R est choisi dans le groupe formé par un atome d'hydrogène et des groupes alkyle, cycloalkyle, cycloalkylalkyle, aryle, aralkyle, aminoalkyle, et des radicaux o-hydroxybenzyle, et $R_1$, $R'_1$, $R_2$, $R'_2$, $R_3$, $R'_3$, $R_4$, $R'_4$, $R_5$, $R'_5$, $R_6$, $R'_6$, $R_7$, $R'_7$, $R_8$, $R'_8$, $R_9$, $R'_9$, $R_{10}$, $R'_{10}$ et R' représentent de l'hydrogène.

3. Composition selon la revendication 2, dans laquelle R est choisi dans le groupe formé par l'hydrogène et les radicaux méthyle, isobutyle, propargyle, cyclohexylméthyle, benzyle, phényle, cyclohexyle, 4-benzyloxybenzyle, o-hydroxybenzyle, aminobutyle et octadécyle.

4. Composition selon la revendication 1, dans laquelle au moins l'un de $R_1$ ou $R'_1$ et $R_2$ ou $R'_2$, $R_3$ ou $R'_3$ et $R_4$ ou $R'_4$, $R_3$ ou $R'_3$ et $R_5$ ou $R'_5$, $R_4$ ou $R'_4$ et $R_5$ ou $R'_5$, $R_6$ ou $R'_6$ et $R_7$ ou $R'_7$, $R_8$ ou $R'_8$ et $R_9$ ou $R'_9$ et $R_{10}$ ou $R'_{10}$ et R ou R' forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau cyclique saturé, partiellement saturé ou insaturé, comprenant de 3 à 20 atomes de carbone, ou au moins l'un de R ou R'. et $R_1$ ou $R'_1$, $R_2$ ou $R'_2$ et $R_3$ ou $R'_3$ ou $R_4$ ou $R'_4$, ou $R_4$ ou $R'_4$ ou $R_5$ ou $R'_5$ et $R_6$ ou $R'_6$, $R_7$ ou $R'_7$ et $R_8$ ou $R'_8$, et $R_9$ ou $R'_9$ et $R_{10}$ ou $R'_{10}$, forment ensemble avec l'atome de carbone auquel ils sont attachés un hétérocycle contenant de l'azote et comprenant de 2 à 20 atomes de carbone ; et tous les groupes "R" restants sont choisis, indépendamment, parmi l'hydrogène et des groupes alkyle.

5. Composition selon la revendication 4, dans laquelle au moins l'un de $R_1$ ou $R'_1$ et $R_2$ ou $R'_2$, $R_3$ ou $R'_3$ et $R_4$ ou $R'_4$, $R_3$ ou $R'_3$ et $R_5$ ou $R'_5$, $R_4$ ou $R'_4$ et $R_5$ ou $R'_5$, $R_6$ ou $R'_6$ et $R_7$ ou $R'_7$, $R_8$ ou $R'_8$ et $R_9$ ou $R'_9$ et $R_{10}$ ou $R'_{10}$ et R ou R' forment ensemble avec l'atome de carbone auquel ils sont attachés un groupe cyclohexano, et tous les groupes "R" restants représentent l'hydrogène ou des groupes alkyle.

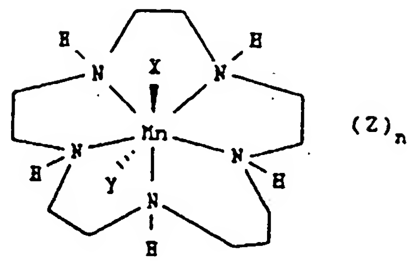
6. Composition selon la revendication 1, dans laquelle X, Y et Z sont choisis, indépendamment, dans le groupe formé par les anions halogénure, acide organique, nitrate et bicarbonate.

7. Utilisation d'un complexe selon la revendication 1 pour la préparation de médicaments destinés à prévenir ou à traiter une maladie ou un désordre de santé dans lequel un superoxyde intervient, au moins en partie, comme médiateur.

8. Utilisation selon la revendication 7, dans laquelle ladite maladie ou désordre de santé est choisi parmi les suivants : lésion ischémique de reperfusion, infarctus du myocarde, métastase, hypertension, ischémie induite par chirurgie, maladie inflammatoire de l'intestin, arthrite rhumatoïde, athérosclérose, thrombose, aggrégation de plaquettes, lésions et accidents des tissus induits par un oxydant, ostéo-arthritise, psoriasis, rejets d'organes transplantés, impuissance, lésions provoquées par des radiations, asthme, grippe, coups de sang, brûlures, trauma, pancréatite aiguë, pyélonéphrite, hépatite, maladies auto-immunitaires, mellitus diabétique insulodépendant, coagulation intravasculaire disséminée, embolie grasse, angoisse respiratoire chez l'adulte et l'enfant, carcinogénèse et hémorragie chez le nouveau-né.

9. Utilisation selon la revendication 8, dans laquelle ladite maladie ou désordre de santé est choisi parmi la lésion ischémique de reperfusion, l'infarctus du myocarde, le coup de sang et l'athérosclérose.

10. Utilisation selon la revendication 9, dans laquelle ledit complexe est représenté par la formule



11. Utilisation selon la revendication 10, lorsque n représente 0 et X et Y représentent Cl.

12. Utilisation d'une composition selon la revendication 1 pour la préparation de médicaments pour la prévention ou le traitement d'une maladie ou d'un désordre de santé dans lequel intervient en tant que médiateur, au moins en partie, un superoxyde ou des radicaux oxygènés dérivés de superoxyde.